

CONFIDENTIAL TREATMENT REQUESTED BY REVOLUTION MEDICINES, INC.
PURSUANT TO 17 C.F.R. Section 200.83

Confidential Draft submitted to the Securities and Exchange Commission on June 8, 2020.
This draft registration statement has not been filed publicly with the Securities and Exchange Commission and all information contained herein remains confidential.
Registration No. 333-

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

**FORM S-1
REGISTRATION STATEMENT**
*Under
The Securities Act of 1933*

Revolution Medicines, Inc.

(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

2836
(Primary Standard Industrial
Classification Code Number)
700 Saginaw Drive
Redwood City, California 94063
(650) 481-6801

47-2029180
(I.R.S. Employer
Identification Number)

(Address, including zip code, and telephone number, including area code, of Registrant's principal executive offices)

Mark A. Goldsmith, M.D., Ph.D.
President and Chief Executive Officer
Revolution Medicines, Inc.
700 Saginaw Drive
Redwood City, California 94063
(650) 481-6801

(Name, address, including zip code, and telephone number, including area code, of agent for service)

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Approximate date of commencement of proposed sale to the public: **As soon as practicable after the effective date of this registration statement.**

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, check the following box.

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a post-effective amendment filed pursuant to Rule 462(d) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

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

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

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided to Section 7(a)(2)(B) of the Securities Act.

CALCULATION OF REGISTRATION FEE

Title of each class of securities to be registered	Amount to be registered(1)	Proposed maximum aggregate offering price per share	Proposed maximum aggregate offering price(2)	Amount of registration fee
Common Stock, \$0.0001 par value per share		\$	\$	\$

(1) Includes shares of common stock that the underwriters have the option to purchase.

(2) Estimated solely for the purpose of calculating the amount of the registration fee in accordance with Rule 457(a) under the Securities Act of 1933, as amended.

The Registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment which specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 or until the Registration Statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

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The information in this preliminary prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This preliminary prospectus is not an offer to sell these securities and is not soliciting an offer to buy these securities in any jurisdiction where such offer or sale is not permitted.

Subject to completion, dated _____, 2020

Preliminary prospectus

shares



Common stock

We are offering _____ shares of our common stock.

Our common stock is listed on the Nasdaq Global Select Market under the symbol "RVMD." The last reported sale price of our common stock on the Nasdaq Global Select Market on _____, 2020 was \$ _____ per share. The final public offering price will be determined through negotiation between us and the lead underwriters in the offering and the recent market price used throughout this prospectus may not be indicative of the final offering price.

We are an "emerging growth company" as defined under the federal securities laws and, as such, have elected to comply with certain reduced public company reporting requirements for this prospectus and may elect to do so in future filings.

	Per share	Total
Public offering price	\$	\$
Underwriting discounts(1)	\$	\$
Proceeds, before expenses, to us	\$	\$

(1) See the section titled "Underwriting" for additional information regarding compensation payable to the underwriters.

We have granted the underwriters an option to purchase up to an additional _____ shares from us at the public offering price less the underwriting discounts and commissions. The underwriters may exercise this right at any time within 30 days after the date of this prospectus.

Investing in our common stock involves a high degree of risk. See the section titled "[Risk factors](#)" beginning on page 11 of this prospectus to read about factors you should consider before buying shares of our common stock.

Neither the Securities and Exchange Commission nor any other 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 underwriters expect to deliver the shares against payment on _____, 2020.

Prospectus dated _____, 2020

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Neither we nor the underwriters have authorized anyone to provide you with information that is different from that contained or incorporated by reference in this prospectus or in any free writing prospectus we may authorize to be delivered or made available to you. We 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 and the underwriters are offering to sell shares of common stock and seeking offers to buy shares of common stock only in jurisdictions where offers and sales are permitted. The information contained or incorporated by reference in this prospectus is accurate only as of the date on the front of this prospectus, or other earlier date stated in this prospectus, regardless of the time of delivery of this prospectus or any sale of shares of our common stock. Our business, financial condition, results of operations and prospects may have changed since that date.

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

Revolution Medicines® and our logo are some of our trademarks used in this prospectus. This prospectus also includes trademarks, tradenames and service marks that are the property of other organizations. Solely for convenience, our trademarks, service marks and tradenames referred to in this prospectus may appear without the ® and ™ symbol, but those references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights, or the right of the applicable licensor to these trademarks, service marks and tradenames.

Prospectus summary

This summary highlights information contained elsewhere in this prospectus. This summary does not contain all of the information you should consider before investing in our common stock. You should read this entire prospectus carefully, including information in our filings with the Securities and Exchange Commission, or SEC, incorporated by reference in this prospectus, before deciding to invest in our common stock. You should carefully consider the information set forth in our consolidated financial statements and the related notes thereto and the information in the section entitled "Risk factors." As used in this prospectus, unless the context otherwise requires, references to "we," "us," "our," "our company," "the Company" and "Revolution Medicines" refer to Revolution Medicines, Inc. and its subsidiary taken as a whole.

Overview

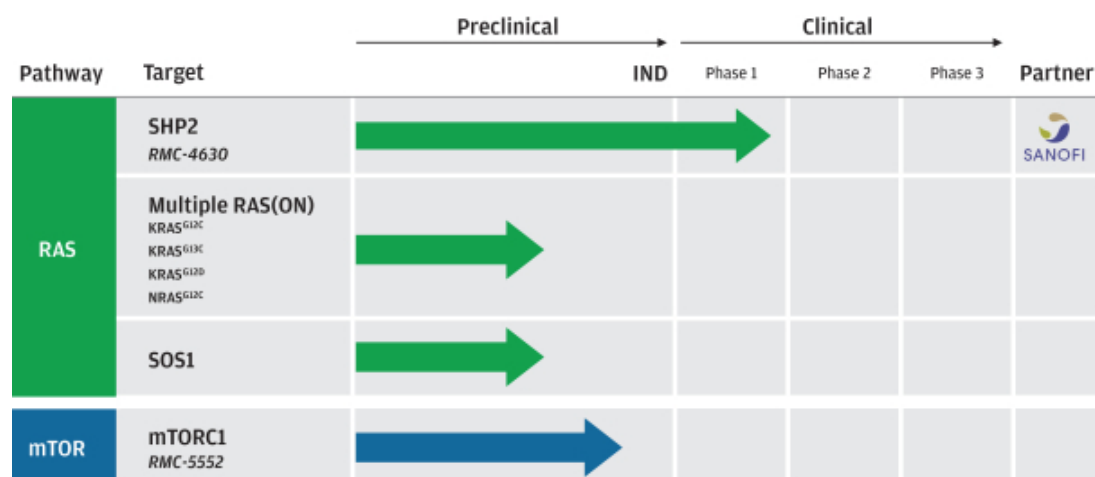
We are a clinical-stage precision oncology company focused on developing novel targeted therapies to inhibit elusive, high-value *frontier* targets within notorious growth and survival pathways, with particular emphasis on the RAS and mTOR signaling pathways. We define *frontier* targets as proteins that play an important role in cancer and for which there is either: no approved drug that directly inhibits it, or one or more approved drugs that directly inhibit it but through a mechanism of action that may not enable suppression of the full range of its biologic contributions to cancer.

Our understanding of genetic drivers and adaptive resistance mechanisms in cancer, coupled with robust drug discovery and medicinal chemistry capabilities, has guided us to establish a deep pipeline targeting critical signaling nodes within these pathways. This cohesive approach underpins our clinical strategy of exploring mechanism-based dosing paradigms and in-pathway combinations to optimize treatment for cancer patients. Our most advanced product candidate, RMC-4630, is a potent and selective inhibitor of SHP2, based on preclinical evidence described in this prospectus under the heading "Business—Our pipeline—Our SHP2 inhibitor, RMC-4630—Preclinical profile of RMC-4630." SHP2 is a central node in the RAS signaling pathway.

In collaboration with Sanofi, we are evaluating RMC-4630 in a multi-cohort Phase 1/2 clinical program. This RMC-4630 Phase 1/2 program currently consists of three active clinical trials: (i) RMC-4630-01, a Phase 1 study of RMC-4630 as a single agent, (ii) RMC-4630-02, a Phase 1b/2 study of RMC-4630 in combination with the MEK inhibitor cobimetinib (Cotellic), and (iii) a Phase 1b study of RMC-4630 in combination with the KRAS^{G12C}(OFF) inhibitor AMG 510, or sotorasib, being sponsored by Amgen as part of its Codebreak 101 study.

In this prospectus, we summarize preliminary data from 87 patients who had enrolled in our Phase 1 study and received RMC-4630 as a monotherapy as of May 4, 2020. In addition, we report preliminary data from eight patients who had been enrolled in our Phase 1b/2 study of RMC-4630 in combination with the MEK inhibitor cobimetinib, had received study medication at the first dose level and were evaluable for safety as of November 14, 2019. Leveraging our proprietary tri-complex technology platform, we are also developing a portfolio of mutant-selective RAS inhibitors that we believe are the first potent, selective, cell-active inhibitors of the active, GTP-bound form of RAS, or RAS(ON). These inhibitors also have exhibited anti-tumor activity *in vivo* in preclinical models. Initially, we will prioritize four mutant RAS(ON) targets—KRAS^{G12C}, KRAS^{G13C}, KRAS^{G12D} and NRAS^{G12C}—and expect to nominate our first development candidate in 2020. Our pipeline also includes inhibitors of other key nodes within the RAS and mTOR signaling pathways, such as SOS1 and mTORC1. Our pipeline includes one product candidate that is in clinical development and all of our other programs are in the preclinical stage. We believe our deep, differentiated pipeline and development strategies provide us with the opportunity to pioneer novel treatment regimens to maximize the depth and durability of clinical benefit and circumvent adaptive resistance mechanisms for patients with cancers dependent on these critical pathways.

The following table summarizes our pipeline.



Under our collaboration on our SHP2 program with Sanofi, we have a 50-50 profit share and a co-promote right in the United States and are eligible to receive royalties on net sales outside of the United States. Sanofi is responsible for reimbursing substantially all of our research costs and all of our development costs for the SHP2 program. For all other programs, we retain worldwide commercial rights.

Our opportunity and innovation engine

We have built an innovation engine that enables us to discover and develop novel targeted therapies for elusive high-value frontier cancer targets with particular focus on a cohesive set of disease targets within notorious growth and survival pathways. This engine consists of three complementary drivers:

- Deep **chemical biology and cancer pharmacology know-how**, including assays and proprietary tool compounds, to define the critical vulnerabilities of “frontier” RAS and mTOR pathway targets and associated signaling circuits in cancer cells;
- Sophisticated **structure-based drug discovery capabilities**, including proven **access to complex chemical space**, to create drug candidates tailored to unconventional binding sites on elusive cancer targets; and
- Astute **precision medicine approach**, embracing patient selection and innovative single agent and combination drug regimens, to translate our preclinical insights into clinical benefit for patients with genetically-defined cancers that are addicted to these pathways.

Our product candidates

RMC-4630, a SHP2 inhibitor

Our most advanced product candidate, RMC-4630, is a potent and selective inhibitor of SHP2, based on preclinical evidence described in this prospectus. SHP2 is a protein that plays a central role in modulating cell survival and growth by transmitting signals from upstream receptor tyrosine kinases, or RTKs, to RAS. In collaboration with Sanofi, we are evaluating RMC-4630 in a multi-cohort Phase 1/2 clinical program. This RMC-4630 Phase 1/2 program currently consists of three active clinical trials: (i) RMC-4630-01, a Phase 1 study

of RMC-4630 as a single agent, RMC-4630-02, (ii) a Phase 1b/2 study of RMC-4630 in combination with the MEK inhibitor cobimetinib, and (iii) a Phase 1b study of RMC-4630 in combination with the KRAS^{G12C}(OFF) inhibitor sotorasib, being sponsored by Amgen. In this prospectus, we report preliminary data from 87 patients who had enrolled in our Phase 1 study and received RMC-4630 as a monotherapy as of May 4, 2020. In addition, we report preliminary data from eight patients who had been enrolled in our Phase 1b/2 study of RMC-4630 in combination with cobimetinib, had received study medication at the first dose level and were evaluable for safety as of November 14, 2019.

The RMC-4630-01 study is evaluating the safety, tolerability, pharmacokinetics and pharmacodynamic effects of RMC-4630 as a single agent under two different dosing schedules: daily and twice weekly intermittent schedules. 49 patients were treated with the daily schedule and 38 patients were treated on an intermittent schedule. Although both dosing regimens have been reasonably well tolerated, daily dosing has been associated with more frequent and severe adverse events than the intermittent schedule. Adverse events in both schedules were consistent with the expected mechanistic effects of the product candidate; including anemia, thrombocytopenia, edema, fatigue and diarrhea.

The RMC-4630-02 study is evaluating the safety, tolerability and pharmacokinetics of RMC-4630 and cobimetinib using intermittent dosing of RMC-4630 with daily dosing of cobimetinib. Adverse events were consistent with the expected mechanistic effects of both SHP2 inhibition and MEK inhibition and are similar in nature to those observed in the RMC-4630-01 study, including edema, diarrhea and other gastrointestinal toxicity, anemia and rash. An alternative schedule using intermittent dosing of both RMC-4630 and cobimetinib is being evaluated.

We also plan to explore the potential clinical benefit of RMC-4630 in combination with other in-pathway agents such as RTK (initially EGFR) and other KRAS^{G12C} inhibitors, including our own KRAS^{G12C}(ON) inhibitors, as well as in combination with PD-1 inhibitors.

Although we are at an early stage of clinical testing and product candidate development, we believe RMC-4630 is well-positioned to become the backbone of targeted therapy combinations for the treatment of various RAS-dependent tumors.

RAS(ON) portfolio

We are also developing a portfolio of what we believe to be the first potent, selective and cell-active inhibitors of mutant RAS(ON) proteins. Historically, direct inhibition of any RAS protein has been challenging due to a lack of tractable, or “druggable,” binding pockets. Recently, selective inhibitors of inactive, GDP-bound forms of RAS, or RAS(OFF), have demonstrated encouraging preliminary anti-tumor effects and thus provide clinical validation for targeting mutant RAS in cancer. Our small molecule inhibitors of mutant RAS(ON) are derived from our proprietary tri-complex technology platform, which enables us to target proteins lacking intrinsic drug binding sites by inducing new druggable pockets. In tumor cells that are addicted to high levels of RAS activation, we believe that selective inhibitors of RAS(ON) will suppress cell growth and survival and be less susceptible to adaptive resistance mechanisms recognized for RAS(OFF) inhibitors. Initially, we will prioritize four mutant RAS(ON) targets—KRAS^{G12C}, KRAS^{G13C}, KRAS^{G12D} and NRAS^{G12C}—and expect to nominate our first development candidate in 2020. We plan to evaluate our RAS(ON) inhibitors alone and in combination with other approved drugs and investigational new drugs, particularly in-pathway agents. We believe that targeted inhibition of various oncogenic RAS(ON) mutants represents a highly differentiated approach for treating the large population of patients with diverse RAS mutations, including non-small cell lung cancer, or NSCLC, colorectal, pancreatic and other cancers.

SOS1 and 4EBP1/mTORC1 programs

We have two preclinical programs targeting other key nodes in the RAS and mTOR signaling pathways. Our program targeting SOS1, a protein that plays a key role in converting RAS(OFF) to RAS(ON) in cells, is currently in lead optimization stage. In addition, our preclinical development candidate, RMC-5552, is designed to selectively and deeply inhibit mTORC1, thereby preventing phosphorylation and inactivation of 4EBP1, a downstream protein in the mTOR signaling pathway that normally suppresses expression of certain oncogenes such as C-MYC. mTORC1-selective inhibitors from our proprietary series, including RMC-5552, have recently been shown to have combinatorial activity with KRAS^{G12C} inhibitors in preclinical models of KRAS^{G12C} lung and colon cancer, suggesting that RMC-5552 is a significant and rational addition to our portfolio of RAS pathway inhibitors. We advanced RMC-5552 into IND-enabling development in June 2019.

Our team

Our management team has significant experience in oncology and in progressing products from early stage research to clinical trials, and ultimately to regulatory approval and commercialization. Dr. Steve Kelsey, our President of Research and Development, was previously President of Onkaido Therapeutics, a Moderna venture focused on oncology mRNA therapeutics, and has held senior positions at Medivation, Geron and Genentech, where he played a significant role in the development of Perjeta, Kadcyla and Erivedge. Our President and Chief Executive Officer, Dr. Mark Goldsmith, served as Chief Executive Officer of Constellation Pharmaceuticals, where he led the creation of its oncology pipeline and drove the development of a strategic alliance with Genentech. He also has led four other companies spanning early discovery through development, including Global Blood Therapeutics, where he led the discovery and early development of voxelotor. Our company was founded and continues to be supported by three world-class scientific advisors: Dr. Kevan Shokat (Professor and Chair of the Department of Cellular and Molecular Pharmacology at University of California, San Francisco, Professor of Chemistry at the University of California, Berkeley and an investigator at the Howard Hughes Medical Institute), Dr. Martin Burke (Professor of Chemistry at the University of Illinois at Urbana-Champaign) and Dr. Michael Fischbach (Associate Professor in the Department of Bioengineering at Stanford University and a Stanford ChEM-H Institute Scholar). Dr. Shokat is widely recognized for his seminal contributions to the field of kinase biology, using chemistry, protein engineering and genetic tools to pioneer novel therapeutic approaches to target key signaling pathways in cancer. He led the discovery of the first KRAS^{G12C}(OFF) inhibitor.

Our strategy

Our goal is to develop novel targeted therapies to outsmart cancer for the benefit of patients. We plan to pursue the following strategies:

- Deploy our innovation engine against *frontier* oncology targets;
- Establish our proprietary SHP2 inhibitor, RMC-4630, as the backbone of targeted therapy combinations for the treatment of RAS-dependent tumors;
- Pioneer mutant selective RAS(ON) inhibition across multiple genetically defined cancers;
- Maximize the global value of our programs by continuing to execute synergistic and value-creating transactions; and
- Maintain our culture of tireless commitment to patients.

Risks related to our business

Our ability to execute our business strategy is subject to numerous risks, including those described in the section titled “Risk factors” immediately following this prospectus summary. These risks include the following, among others:

- We are a clinical-stage precision oncology company with a limited operating history and no products approved for commercial sale. We have incurred significant losses since inception. We expect to incur losses for at least the next several years and may never achieve or maintain profitability, which, together with our limited operating history, makes it difficult to assess our future viability.
- We have never generated revenue from product sales and may never be profitable.
- Even if this offering is successful, we will require substantial additional financing to achieve our goals, which may not be available on acceptable terms, or at all. A failure to obtain this necessary capital when needed could force us to delay, limit, reduce or terminate our product development or commercialization efforts.
- We are early in our development efforts. Our business is dependent on the successful development of our current and future product candidates. If we are unable to advance our current or future product candidates through clinical trials, obtain marketing approval and ultimately commercialize any product candidates we develop, or experience significant delays in doing so, our business will be materially harmed.
- If we encounter difficulties enrolling patients in our clinical trials, our clinical development activities could be delayed or otherwise be adversely affected.
- We are dependent on our collaboration with Sanofi for the development of RMC-4630 and may depend on Sanofi for the development and commercialization of any other future SHP2 inhibitor product candidates. Under certain circumstances, Sanofi may unilaterally terminate the collaboration for convenience, which would materially and adversely affect our business.
- We are developing RMC-4630 in combination with Roche’s cobimetinib, Amgen’s investigational KRAS^{G12C}(OFF) inhibitor, sotorasib and may, in the future, develop RMC-4630 and other product candidates in combination with other therapies, which exposes us to additional risks.
- We face significant competition, and if our competitors develop and market products that are more effective, safer or less expensive than the product candidates we develop, our commercial opportunities will be negatively impacted.
- If we and our collaborators are unable to obtain and maintain sufficient patent and other intellectual property protection for our product candidates and technology, our competitors could develop and commercialize products and technology similar or identical to ours, and we may not be able to compete effectively in our market or successfully commercialize any product candidates we may develop.
- Epidemic and pandemic diseases, such as COVID-19, or the perception of their effects, could have a material adverse effect on our business, financial condition, results of operations or cash flows.

Corporate information

We were founded in October 2014 as a Delaware corporation. Our principal executive offices are located at 700 Saginaw Drive, Redwood City, California 94063, and our telephone number is (650) 481-6801.

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Our website address is www.revmed.com. The information on, or that can be accessed through, our website is not part of this prospectus and is not incorporated by reference herein. We have included our website address as an inactive textual reference only.

Implications of being an emerging growth company

We are an emerging growth company as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. We will remain an emerging growth company until the earliest of: (1) December 31, 2025, (2) the last day of the fiscal year in which we have total annual gross revenue of at least \$1.07 billion, (3) the last day of the fiscal year in which we are deemed to be a "large accelerated filer" as defined in Rule 12b-2 under the Securities Exchange Act of 1934, as amended, or the Exchange Act, which would occur if the market value of our common stock held by non-affiliates exceeded \$700.0 million as of the last business day of the second fiscal quarter of such year or (4) the date on which we have issued more than \$1.0 billion in non-convertible debt securities during the prior three-year period. An emerging growth company may take advantage of specified reduced reporting requirements and is relieved of certain other significant requirements that are otherwise generally applicable to public companies. As an emerging growth company:

- We will avail ourselves of the exemption from the requirement to obtain an attestation and report from our independent registered public accounting firm on the assessment of our internal control over financial reporting pursuant to the Sarbanes-Oxley Act of 2002;
- We will provide less extensive disclosure about our executive compensation arrangements; and
- We will not require stockholder non-binding advisory votes on executive compensation or golden parachute arrangements.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This provision allows an emerging growth company to delay the adoption of some accounting standards until those standards would otherwise apply to private companies. We have elected to use the extended transition period for any other new or revised accounting standards during the period in which we remain an emerging growth company; however, we may adopt certain new or revised accounting standards early.

The offering

Common stock offered by us	shares
Underwriters' option to purchase additional shares from us	We have granted the underwriters a 30-day option to purchase up to additional shares at the public offering price, less underwriting discounts and commissions.
Common stock to be outstanding immediately after this offering	shares (or shares if the underwriters exercise in full their option to purchase additional shares)
Use of proceeds	<p>We estimate that the net proceeds from this offering will be approximately \$ million, or approximately \$ million if the underwriters exercise their option to purchase additional shares in full, at the public offering price of \$ per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on , 2020, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.</p> <p>We currently expect to use the net proceeds from this offering, together with our existing cash, cash equivalents and marketable securities, to fund the development of our multiple RAS programs, including our RAS(ON) portfolio and our SOS1 program, and our 4EBP1/mTORC1 program and other general corporate purposes, which may include the hiring of additional personnel, capital expenditures and the costs of operating as a public company. See "Use of proceeds" on page 75 for a more complete description of the intended use of proceeds from this offering.</p>
Risk factors	See "Risk factors" beginning on page 11 and other information included or incorporated by reference in this prospectus for a discussion of factors that you should consider carefully before deciding to invest in our common stock.
Nasdaq Global Select Market symbol	"RVMD"

The number of shares of common stock to be outstanding after this offering is based on 59,003,644 shares of common stock outstanding as of March 31, 2020, and excludes the following:

- 5,568,324 shares of common stock issuable upon the exercise of outstanding stock options as of March 31, 2020 having a weighted-average exercise price of \$5.29 per share;
- shares of common stock issuable upon the exercise of stock options granted after March 31, 2020 having a weighted-average exercise price of \$ per share;
- 5,110,075 shares of common stock reserved for issuance pursuant to future awards under our 2020 Incentive Award Plan, as well as any automatic increases in the number of shares of common stock reserved for future issuance under this plan; and

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- 528,959 shares of common stock reserved for issuance under our 2020 Employee Stock Purchase Plan, as well as any automatic increases in the number of shares of our common stock reserved for future issuance under this plan.

In addition, unless we specifically state otherwise, all information in this prospectus reflects and assumes the following:

- no exercise of outstanding stock options subsequent to March 31, 2020; and
- no exercise of the underwriters' option to purchase additional shares of common stock.

Summary consolidated financial data

The following tables present our summary consolidated financial data for the periods and as of the dates indicated. You should read this data together with our consolidated financial statements and related notes incorporated by reference in this prospectus and the information under the captions "Selected consolidated financial data" appearing in our Annual Report on Form 10-K for the fiscal year ended December 31, 2019, or our 2019 Annual Report, and "Management's discussion and analysis of financial condition and results of operations" appearing in our 2019 Annual Report and in our Quarterly Report on Form 10-Q for the quarter ended March 31, 2020, or our March 2020 Quarterly Report, which are incorporated by reference herein.

We have derived the following consolidated statement of operations data for the years ended December 31, 2017, 2018 and 2019 from our audited consolidated financial statements and related notes incorporated by reference herein from our 2019 Annual Report. The summary consolidated statements of operations data for the three months ended March 31, 2019 and 2020 and the summary consolidated balance sheet data as of March 31, 2020 are derived from our unaudited interim consolidated financial statements incorporated by reference herein from our March 2020 Quarterly Report. The unaudited interim financial statements have been prepared in accordance with generally accepted accounting principles in the United States and on the same basis as the audited consolidated financial statements and, in the opinion of management, reflect all adjustments, which include only normal recurring adjustments, necessary to state fairly our financial position as of March 31, 2020 and the results of operations for the three months ended March 31, 2019 and 2020. Our historical results are not necessarily indicative of our future results and results for the three months ended March 31, 2020 are not necessarily indicative of results to be expected for the full year.

	Year ended December 31,			Three months ended March 31,	
	2017	2018	2019	2019	2020
	(in thousands, except share and per share data)				
Consolidated Statement of Operations Data:					
Revenue:					
Collaboration revenue, related party	\$ —	\$ 19,420	\$ 50,041	\$ 13,166	\$ 11,546
Collaboration revenue, other	—	745	—	—	—
Total revenue	—	20,165	50,041	13,166	11,546
Operating expenses:					
Research and development	26,586	51,084	91,755	21,186	27,457
General and administrative	4,543	9,410	12,406	2,416	5,171
Total operating expenses	31,129	60,494	104,161	23,602	32,628
Loss from operations	(31,129)	(40,329)	(54,120)	(10,436)	(21,082)
Other income (expense), net:					
Interest income	105	777	2,189	335	909
Interest and other expense	(103)	(116)	(106)	(30)	(21)
Change in fair value of redeemable convertible preferred stock liability	—	(2,121)	—	—	—
Total other income (expense), net	2	(1,460)	2,083	305	888
Los before income taxes	\$ (31,127)	\$ (41,789)	\$ (52,037)	\$ (10,131)	\$ (20,194)
Benefit from income taxes	—	—	4,373	—	675
Net loss	\$ (31,127)	\$ (41,789)	\$ (47,664)	\$ (10,131)	\$ (19,519)
Redeemable convertible preferred stock dividends—undeclared and cumulative	(3,763)	(7,031)	(14,238)	(2,676)	(2,219)
Net loss attributable to common stockholders	\$ (34,890)	\$ (48,820)	\$ (61,902)	\$ (12,807)	\$ (21,738)
Net loss per share attributable to common stockholders—basic and diluted(1)	\$ (20.25)	\$ (21.24)	\$ (22.33)	\$ (4.84)	\$ (0.74)
Weighted-average shares used to compute net loss per share attributable to common stockholders—basic and diluted(1)	1,723,827	2,298,820	2,772,589	2,643,649	29,297,698

(1) For the calculation of our basic and diluted net loss per share attributable to common stockholders and weighted-average number of shares used in the computation of the per share amounts, see Note 14 to our consolidated financial statements included in our 2019 Annual Report incorporated by reference herein and Note 12 to our unaudited interim condensed consolidated financial statements included in our March 2020 Quarterly Report incorporated by reference in this prospectus.

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	As of March 31, 2020	
	Actual	As adjusted(1)
(in thousands)		
Consolidated Balance Sheet Data:		
Cash, cash equivalents and marketable securities	\$347,948	
Working capital(2)	320,572	
Total assets	454,341	
Total liabilities	69,025	
Accumulated deficit	176,905	
Total stockholders' equity	385,316	

(1) Each \$1.00 increase (decrease) in the assumed public offering price of \$ per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on , 2020, would increase (decrease) the amount of each of cash, cash equivalents and marketable securities, working capital, total assets and total stockholders' equity by \$ million, assuming the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same and after deducting the underwriting discount and commissions and estimated offering expenses payable by us. We may also increase (decrease) the number of shares we are offering. Each increase (decrease) of 1,000,000 in the number of shares we are offering would increase (decrease) the amount of each of cash, cash equivalents and marketable securities, working capital, total assets and total stockholders' equity by approximately \$ million, assuming the assumed public offering price of \$ per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on , 2020, remains the same and after deducting the underwriting discount and commissions and estimated offering expenses payable by us. The as adjusted information is illustrative only and we will adjust this information based on the actual public offering price and other terms of this offering determined at pricing.

(2) We define working capital as current assets less current liabilities. See our unaudited interim consolidated financial statements incorporated by reference in this prospectus for details regarding our current assets and current liabilities.

The preceding table presents our consolidated balance sheet data as of March 31, 2020:

- on an actual basis;
- on an as adjusted basis to give effect to the sale of shares of common stock in this offering at the assumed public offering price of \$ per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on , 2020, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

Risk factors

Investing in our common stock involves a high degree of risk. You should carefully consider the risks described below, as well as the other information in this prospectus or incorporated by reference herein before deciding whether to invest in our common stock. The occurrence of any of the events or developments described below could harm our business, financial condition, results of operations and growth prospects. In such an event, the market price of our common stock could decline, and you may lose all or part of your investment. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also impair our business operations.

Risks related to our limited operating history, financial position and need for additional capital

We are a clinical-stage precision oncology company with a limited operating history and no products approved for commercial sale. We have incurred significant losses since inception. We expect to incur losses for at least the next several years and may never achieve or maintain profitability, which, together with our limited operating history, makes it difficult to assess our future viability.

Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. We are a clinical-stage precision oncology company, and we have only a limited operating history upon which you can evaluate our business and prospects. We currently have no products approved for commercial sale, have not generated any revenue from sales of products and have incurred losses in each year since our inception in October 2014. In addition, we have limited experience as a company and have not yet demonstrated an ability to successfully overcome many of the risks and uncertainties frequently encountered by companies in new and rapidly evolving fields, particularly in the biopharmaceutical industry. Only one of our product candidates, RMC-4630, is currently in clinical development.

Since inception, we have incurred significant net losses. Our net losses were \$47.7 million, \$41.8 million, and \$31.1 million for the years ended December 31, 2019, 2018 and 2017, respectively. Our net loss was \$19.5 million for the three months ended March 31, 2020. As of March 31, 2020, we had an accumulated deficit of \$176.9 million. We have funded our operations to date primarily with proceeds from the sale of common stock and preferred stock and upfront payments and research and development cost reimbursement received under our collaboration agreement with Genzyme Corporation, an affiliate of Sanofi, or the Sanofi Agreement. To date, we have devoted substantially all of our resources to organizing and staffing our company, business planning, raising capital, acquiring and discovering development programs, securing intellectual property rights and conducting discovery, research and development activities for our programs. We have not yet demonstrated our ability to successfully complete any clinical trials, including pivotal clinical trials, obtain marketing approvals, manufacture a commercial-scale product, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Our product candidates will require substantial additional development time and resources before we will be able to apply for or receive regulatory approvals and, if approved, begin generating revenue from product sales. We expect to continue to incur significant expenses and operating losses for the foreseeable future.

We have never generated revenue from product sales and may never be profitable.

Our ability to generate revenue from product sales and achieve profitability depends on our ability, alone or with our collaboration partners, to successfully complete the development of, and obtain the regulatory approvals necessary to commercialize, our development programs. We do not anticipate generating revenue

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from product sales for the next several years, if ever. Our ability to generate future revenue from product sales depends heavily on our, Sanofi's, and any potential future collaborators' success in:

- completing clinical and preclinical development of product candidates and programs and identifying and developing new product candidates;
- seeking and obtaining marketing approvals for any product candidates that we develop;
- launching and commercializing product candidates for which we obtain marketing approval by establishing a sales force, marketing, medical affairs and distribution infrastructure or, alternatively, collaborating with a commercialization partner;
- achieving adequate coverage and reimbursement by third-party payors for product candidates that we develop;
- establishing and maintaining supply and manufacturing relationships with third parties that can provide adequate, in both amount and quality, products and services to support clinical development and the market demand for product candidates that we develop, if approved;
- obtaining market acceptance of product candidates that we develop as viable treatment options;
- addressing any competing technological and market developments;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter and performing our obligations in such collaborations;
- maintaining, protecting, enforcing and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how;
- defending against third-party interference, infringement or other intellectual property-related claims, if any; and
- attracting, hiring and retaining qualified personnel.

Even if one or more of the product candidates that we develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate. Our expenses could increase beyond expectations if we are required by the U.S. Food and Drug Administration, or the FDA, the European Medicines Agency, or the EMA, or other regulatory agencies to perform clinical trials or studies in addition to those that we currently anticipate. Even if we are able to generate revenue from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations.

Even if this offering is successful, we will require substantial additional financing to achieve our goals, which may not be available on acceptable terms, or at all. A failure to obtain this necessary capital when needed could force us to delay, limit, reduce or terminate our product development or commercialization efforts.

Our operations have consumed substantial amounts of cash since inception. Since our inception, we have invested a significant portion of our efforts and financial resources in research and development activities for our initial preclinical and clinical product candidates. Preclinical studies and clinical trials and additional research and development activities will require substantial funds to complete. As of March 31, 2020, we had cash, cash equivalents and marketable securities of \$347.9 million. In February 2020, we raised \$250.7 million upon the completion of our initial public offering, or IPO, net of underwriting discounts and commissions and offering expenses. We expect to continue to spend substantial amounts to continue the preclinical and clinical

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development of our current and future programs. If we are able to gain marketing approval for product candidates that we develop, including RMC-4630, we will require significant additional amounts of cash in order to launch and commercialize such product candidates to the extent that such launch and commercialization are not the responsibility of Sanofi or another collaborator that we may contract with in the future. In addition, other unanticipated costs may arise. Because the design and outcome of our planned and anticipated clinical trials is highly uncertain, we cannot reasonably estimate the actual amounts necessary to successfully complete the development and commercialization of any product candidate we develop.

The timing and amount of our future capital requirements depend on many factors, including:

- the scope, progress, results and costs of researching and developing our product candidates and programs, and of conducting preclinical studies and clinical trials;
- the timing of, and the costs involved in, obtaining marketing approvals for product candidates we develop if clinical trials are successful;
- the success of our collaboration with Sanofi, including the continued reimbursement by Sanofi of substantially all of our research costs and all of our development costs for the SHP2 program under the Sanofi Agreement;
- whether we achieve certain clinical and regulatory milestones under the Sanofi Agreement, each of which would trigger additional payments to us;
- the cost of commercialization activities for RMC-4630, to the extent not borne by Sanofi, and any other future product candidates we develop, whether alone or in collaboration, including marketing, sales and distribution costs if RMC-4630 or any other product candidate we develop is approved for sale;
- the cost of manufacturing our current and future product candidates for clinical trials in preparation for marketing approval and in preparation for commercialization;
- our ability to establish and maintain strategic licenses or other arrangements and the financial terms of such agreements;
- the costs involved in preparing, filing, prosecuting, maintaining, expanding, defending and enforcing patent claims, including litigation costs and the outcome of such litigation;
- the timing, receipt and amount of sales of, profit share or royalties on, our future products, if any;
- the emergence of competing cancer therapies and other adverse market developments; and
- any plans to acquire or in-license other programs or technologies.

Other than our Sanofi collaboration on SHP2 inhibitors, including RMC-4630, we do not have any committed external source of funds or other support for our development efforts. We expect to finance our cash needs through a combination of public or private equity offerings, debt financings, collaborations, strategic alliances, licensing arrangements and other marketing or distribution arrangements. In addition, we may seek additional capital due to favorable market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. We believe that the net proceeds from this offering, together with our existing cash, cash equivalents and marketable securities, will enable us to fund our operations for at least 12 months following the date of this offering.

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Our ability to raise additional funds will depend on financial, economic and other factors, many of which are beyond our control. Additional funds may not be available when we need them, on terms that are acceptable to us, or at all. If adequate funds are not available to us on a timely basis, we may be required to:

- delay, limit, reduce or terminate preclinical studies, clinical trials or other research and development activities or eliminate one or more of our development programs altogether; or
- delay, limit, reduce or terminate our efforts to establish manufacturing and sales and marketing capabilities or other activities that may be necessary to commercialize any future approved products, or reduce our flexibility in developing or maintaining our sales and marketing strategy.

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

To date, we have primarily financed our operations through the sale of preferred stock and common stock and upfront payments and research and development cost reimbursement received in connection with our collaboration with Sanofi. We will be required to seek additional funding in the future and currently intend to do so through collaborations, public or private equity offerings or debt financings, credit or loan facilities or a combination of one or more of these funding sources. If we raise additional capital through marketing and distribution arrangements or other collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish certain valuable rights to our product candidates, technologies, future revenue streams or research programs or grant licenses on terms that may not be favorable to us. If we raise additional funds by issuing equity securities, our stockholders may suffer dilution and the terms of any financing may adversely affect the rights of our stockholders. In addition, as a condition to providing additional funds to us, future investors may demand, and may be granted, rights superior to those of existing stockholders. Debt financing, if available, is likely to involve restrictive covenants limiting our flexibility in conducting future business activities, and, in the event of insolvency, debt holders would be repaid before holders of our equity securities would receive any distribution of our corporate assets. Attempting to secure additional financing may also divert our management from our day-to-day activities, which may adversely affect our ability to develop our product candidates.

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

Our quarterly and annual operating results may fluctuate significantly, which will make it difficult for us to predict our future results. These fluctuations may occur due to a variety of factors, many of which are outside of our control and may be difficult to predict, including:

- the timing and cost of, and level of investment in, research, development and commercialization activities, which may change from time to time;
- the timing and status of enrollment for our clinical trials;
- the timing of regulatory approvals, if any, in the United States and internationally;
- the timing of expanding our operational, financial and management systems and personnel, including personnel to support our clinical development, quality control, manufacturing and commercialization efforts and our operations as a public company;
- the cost of manufacturing, as well as building out our supply chain, which may vary depending on the quantity of productions, and the terms of any agreements we enter into with third-party suppliers;
- timing and amount of any milestone, royalty or other payments due under any current or future collaboration or license agreement, including the Sanofi Agreement;

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- coverage and reimbursement policies with respect to any future approved products, and potential future drugs that compete with our products;
- the timing and cost to establish a sales, marketing, medical affairs and distribution infrastructure to commercialize any products for which we may obtain marketing approval and intend to commercialize on our own or jointly with Sanofi;
- expenditures that we may incur to acquire, develop or commercialize additional products and technologies;
- the level of demand for any future approved products, which may vary significantly over time;
- future accounting pronouncements or changes in our accounting policies; and
- the timing and success or failure of preclinical studies and clinical trials for our product candidates or competing product candidates, or any other change in the competitive landscape of our industry, including consolidation among our competitors or collaboration partners.

The cumulative effects of these factors could result in large fluctuations and unpredictability in our quarterly and annual operating results. As a result, comparing our operating results on a period-to-period basis may not be meaningful. Investors should not rely on our past results as an indication of our future performance.

This variability and unpredictability could also result in our failing to meet the expectations of industry or financial analysts or investors for any period. If our revenue or operating results fall below the expectations of analysts or investors or below any forecasts we may provide to the market, or if the forecasts we provide to the market are below the expectations of analysts or investors, the price of our common stock could decline substantially. Such a stock price decline could occur even when we have met any previously publicly stated revenue or earnings guidance we may provide.

Risks related to product development and regulatory process

We are early in our development efforts. Our business is dependent on the successful development of our current and future product candidates. If we are unable to advance our current or future product candidates through clinical trials, obtain marketing approval and ultimately commercialize any product candidates we develop, or experience significant delays in doing so, our business will be materially harmed.

We are early in our development efforts, and we have only recently initiated our first clinical trials for our most advanced product candidate, RMC-4630. Our other programs are in the preclinical stage. We have invested substantially all of our efforts and financial resources in the identification of targets and preclinical development of small molecules to treat cancer.

The success of our business, including our ability to finance our company and generate revenue from products in the future, which we do not expect will occur for several years, if ever, will depend heavily on the successful development and eventual commercialization of the product candidates we develop, which may never occur. Our current product candidates, and any future product candidates we develop, will require additional preclinical and clinical development, management of clinical, preclinical and manufacturing activities, marketing approval in the United States and other markets, demonstrating effectiveness to pricing and reimbursement authorities, obtaining sufficient manufacturing supply for both clinical development and commercial production, building of a commercial organization, and substantial investment and significant marketing efforts before we generate any revenues from product sales.

We have not previously submitted a new drug application, or NDA, to the FDA or similar approval filings to a comparable foreign regulatory authority, for any product candidate. An NDA or other relevant regulatory filing

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must include extensive preclinical and clinical data and supporting information to establish that the product candidate is safe and effective for each desired indication. The NDA or other relevant regulatory filing must also include significant information regarding the chemistry, manufacturing and controls for the product. We cannot be certain that our current or future product candidates will be successful in clinical trials or receive regulatory approval. Further, even if they are successful in clinical trials, our product candidates or any future product candidates may not receive regulatory approval. If we do not receive regulatory approvals for current or future product candidates, we may not be able to continue our operations. Even if we successfully obtain regulatory approval to market a product candidate, our revenue will depend, in part, upon the size of the markets in the territories for which we gain regulatory approval and have commercial rights, as well as the availability of competitive products, whether there is sufficient third-party reimbursement and adoption by physicians.

We plan to seek regulatory approval to commercialize our product candidates both in the United States and in select foreign countries. While the scope of regulatory approval generally is similar in other countries, in order to obtain separate regulatory approval in other countries we must comply with numerous and varying regulatory requirements of such countries regarding safety and efficacy. Other countries also have their own regulations governing, among other things, clinical trials and commercial sales, as well as pricing and distribution of drugs, and we may be required to expend significant resources to obtain regulatory approval and to comply with ongoing regulations in these jurisdictions.

The success of our current and future product candidates will depend on several factors, including the following:

- successful completion of clinical trials and preclinical studies;
- sufficiency of our financial and other resources to complete the necessary preclinical studies and clinical trials;
- acceptance of investigational new drug applications, or INDs, for our planned clinical trials or future clinical trials;
- successful enrollment and completion of clinical trials, particularly where competitors may also be recruiting patients with KRAS^{G12C} mutations;
- successful data from our clinical program that supports an acceptable risk-benefit profile of our product candidates in the intended populations;
- receipt and maintenance of marketing approvals from applicable regulatory authorities;
- establishing agreements with third-party manufacturers for clinical supply for our clinical trials and commercial manufacturing, if one of our product candidates is approved;
- entry into collaborations to further the development of our product candidates;
- obtaining and maintaining our portfolio of intellectual property rights, including patents, trade secrets and know-how;
- enforcing and defending intellectual property rights and claims;
- obtaining and maintaining regulatory exclusivity for our product candidates;
- successfully launching commercial sales of our product candidates, if approved;
- acceptance of the product candidate's benefits and uses, if approved, by patients, the medical community and third-party payors;

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- the prevalence, duration and severity of potential side effects or other safety issues experienced with our product candidates following approval;
- effectively competing with other therapies; and
- obtaining and maintaining healthcare coverage and adequate reimbursement from third-party payors.

If we are not successful with respect to one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize the product candidates we develop, which would materially harm our business. If we do not receive marketing approvals for RMC-4630, or any other product candidate we develop, we may not be able to continue our operations.

Preclinical development is uncertain. Our preclinical programs may experience delays or may never advance to clinical trials, which would adversely affect our ability to obtain regulatory approvals or commercialize our product candidates on a timely basis or at all, which would have an adverse effect on our business.

In order to obtain FDA approval to market a new small molecule product, we must demonstrate proof of safety and efficacy in humans. To meet these requirements, we will have to conduct adequate and well-controlled clinical trials. Before we can commence clinical trials for a product candidate, we must complete extensive preclinical studies that support our planned INDs in the United States. We only have one product candidate in clinical development and the rest of our programs are in preclinical research or development, including our RAS portfolio and RMC-5552 product candidate. We cannot be certain of the timely completion or outcome of our preclinical studies and cannot predict if the FDA will accept our proposed clinical programs or if the outcome of our preclinical studies will ultimately support further development of our programs. As a result, we cannot be sure that we will be able to submit INDs or similar applications on the timelines we expect, if at all, and we cannot be sure that submission of INDs or similar applications will result in the FDA or other regulatory authorities allowing additional clinical trials to begin.

Conducting preclinical testing is a lengthy, time-consuming and expensive process. The length of time may vary substantially according to the type, complexity and novelty of the program, and often can be several years or more per program. Delays associated with programs for which we are directly conducting preclinical studies may cause us to incur additional operating expenses. Moreover, we may be affected by delays associated with the studies of certain programs that are the responsibility of Sanofi or our potential future partners over which we have no control. The commencement and rate of completion of preclinical studies and clinical trials for a product candidate may be delayed by many factors, including, for example:

- inability to generate sufficient preclinical or other *in vivo* or *in vitro* data to support the initiation of clinical studies;
- delays in reaching a consensus with regulatory agencies on study design and obtaining regulatory authorization to commence clinical trials;
- obtaining sufficient quantities of our product candidates for use in preclinical studies and clinical trials from third-party suppliers on a timely basis; and
- delays due to the COVID-19 pandemic, including the implementation of a temporary work from home policy following the California state order for all residents to remain at home, except as needed for essential activities, or reduced workforce resulting from illness, or delays at our third-party contract research organizations throughout the world, due to similar restrictions imposed by governments or reduced workforce resulting from illness.

Moreover, even if clinical trials do begin for our preclinical programs, our development efforts may not be successful, and clinical trials that we conduct or that third parties conduct on our behalf may not demonstrate

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sufficient safety or efficacy to obtain the requisite regulatory approvals for any product candidates we develop. Even if we obtain positive results from preclinical studies or initial clinical trials, we may not achieve the same success in future trials.

Some of our programs focus on the discovery and development of “Beyond Rule of 5” small molecules. Such molecules can be associated with longer development timelines and greater costs compared to traditional small molecule drugs. Our “Beyond Rule of 5” product candidates may take longer to develop and/or manufacture relative to traditional small molecules, and we may not be able to formulate “Beyond Rule of 5” candidates for certain routes of administration.

We enlist various technologies and capabilities that give us chemical access to challenging sites on target proteins that generally are not accessible using conventional small molecule drug discovery approaches. For each target, we consider the specific structural, physico-chemical, functional and dynamic properties of the target and deploy the approach or approaches that appear most likely to yield viable development candidates. The “Rule of 5” is a set of criteria used in pharmaceutical drug development to determine whether chemical compounds have certain physico-chemical properties that make them likely to be orally active drugs in humans. In some instances, the compounds we discover and develop are traditional small molecules (i.e. less than 500 daltons) with properties that generally satisfy conventional pharmaceutical “Rule of 5” criteria, while in other cases, they are larger (i.e. more than 500 daltons) “Beyond Rule of 5”, or BRo5, compounds that by definition do not satisfy these criteria. For example, our mTORC1 program and our RAS(ON) program each include pursuit of BRo5 compounds.

BRo5 compounds have been successfully pursued by many pharmaceutical companies. Examples of BRo5 compounds include natural products and semi-synthetic derivatives, peptidomimetics, macrocycles and degraders. However, larger molecular weight small molecules often cannot be formulated into orally absorbed drugs and also often face solubility, potency, bioavailability and stability challenges, among others. In addition, many of the commonly used predictive and other drug development tools are designed specifically for small molecule drugs rather than larger molecules, contributing to the difficulty and uncertainty of development of BRo5 compounds.

Due to their size and complexity, drug development of our BRo5 compounds may be slower and/or more expensive than drug development of traditional “Rule of 5” compounds, resulting in program delays, increased costs or failure to obtain regulatory approval in a commercially reasonable timeframe, if at all. Our competitors developing traditional small molecules in areas where we are developing BRo5 compounds could obtain regulatory approval and reach the market before we do. Even if we succeed in generating an approved drug from a BRo5 compound, it may be less convenient to administer, have higher grade and/or more frequent side effects or be more costly to manufacture and formulate than competing products on the market. The discovery and development of BRo5 small molecules may pose risks to us such as:

- BRo5 small molecules may present difficult synthetic chemistry and manufacturing challenges, including with any scale-up of our product candidates in sufficient quality and quantity;
- BRo5 small molecules may be challenging to purify, including with any scale-up of our product candidates in sufficient quality and quantity;
- BRo5 small molecules may present solubility challenges in the development of any such small molecules;
- BRo5 small molecules may present oral absorption challenges due to low passive permeability;
- BRo5 small molecules may present cell permeability challenges, especially with regards to lipophilicity, hydrogen bond donor and rotatable bond count, and high topological polar surface area;

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- any BRo5 small molecules we seek to develop may not achieve acceptable oral bioavailability for development and may result in poor pharmaceutical properties for formulation development;
- any BRo5 small molecules we seek to develop may have a propensity to be substrates for efflux proteins such as the adenosine triphosphate (ATP) binding cassette (ABC) transporter protein family, including multidrug resistance protein 1. Cancer cells may overexpress these transporter proteins causing an increase in expulsion of our product candidate from the cell. As the site of action of our product candidates, for example the RAS protein, is inside the cell, expulsion by these transporter proteins may decrease the effective concentration in the cell sufficiently to reduce target inhibition and thereby render a RAS-dependent tumor less susceptible to the inhibitory activity of the product candidate;
- BRo5 small molecules may present central nervous system, or CNS, penetration challenges due to low passive permeability and/or interaction with efflux transporters at the blood brain barrier and this could limit sensitivity of CNS tumors to our product candidates;
- BRo5 small molecules may present formulation vehicle challenges for administration, such as intravenous and subcutaneous administration, due to aspects such as solubility and hydrophobicity;
- BRo5 small molecules may present stability and shelf-life limitations due to the incorporation of labile functionality in our scaffolds, including for example in the development of RMC-5552 which currently requires a cold chain storage of zero degrees Celsius; and
- BRo5 small molecules may present off-target toxicities due to physico-chemical properties such as lipophilicity, which is the ability to dissolve fats, oils and lipids, the presence of off-target pharmacophores in the molecule that can interact with other cellular proteins, or other characteristics that have not been fully characterized within a novel chemical scaffold or platform.

These and other risks related to our research and development of BRo5 small molecules may result in delays in development, an increase in development costs and/or the failure to develop any BRo5 small molecule to approval. As a result, our competitors may develop products more rapidly and cost effectively than we do. In particular, competitors may develop and commercialize a product that competes with a product candidate we may develop from our RAS(ON) program as some of our competitors in this area are pursuing conventional small molecules directed to other forms of RAS, such as RAS(OFF), and are further along in development than we currently are. Any such setbacks in our research and development of a BRo5 small molecule could have a material adverse effect on our business and operating results.

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

The time required to obtain approval by the FDA, the EMA and comparable foreign authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. We have not obtained regulatory approval for any product candidate and it is possible that none of our current or future product candidates will ever obtain regulatory approval.

Our current and future product candidates could fail to receive regulatory approval for many reasons, including the following:

- the FDA, the EMA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials;

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- we may be unable to demonstrate to the satisfaction of the FDA, the EMA or comparable foreign regulatory authorities that a product candidate is safe or effective for its proposed indication or indications;
- the results of clinical trials may not meet the level of statistical significance required by the FDA, the EMA or comparable foreign regulatory authorities for approval;
- we may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- the FDA, the EMA or comparable foreign regulatory authorities may disagree with our interpretation of data from clinical trials or preclinical studies;
- the data collected from clinical trials of our product candidates may not be sufficient to support the submission of an NDA to the FDA or other submission or to obtain regulatory approval in the United States, the European Union or elsewhere;
- the FDA, the EMA or comparable foreign regulatory authorities may find deficiencies with or fail to approve the manufacturing processes or facilities of third-party manufacturers with which we contract for clinical and commercial supplies; and
- the approval policies or regulations of the FDA, the EMA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

This lengthy approval process as well as the unpredictability of clinical trial results may result in our failing to obtain regulatory approval to market any product candidate we develop, which would significantly harm our business, results of operations and prospects. The FDA, the EMA and other comparable foreign authorities have substantial discretion in the approval process, and determining when or whether regulatory approval will be obtained for any product candidate that we develop. Even if we believe the data collected from future clinical trials of our product candidates are promising, such data may not be sufficient to support approval by the FDA, the EMA or any other regulatory authority.

In addition, even if we were to obtain approval, regulatory authorities may approve any of our product candidates for fewer or more limited indications than we request, may not approve the price we intend to charge for our products, may grant approval contingent on the performance of costly post-marketing clinical trials, or may approve a product candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates.

Further, we have not previously submitted a NDA to the FDA, or a Marketing Authorization Application, or MAA, to the EMA. We cannot be certain that any of our programs will be successful in clinical trials or receive regulatory approval. Further, product candidates we develop may not receive regulatory approval even if they are successful in clinical trials. If we do not receive regulatory approvals for our product candidates, we may not be able to continue our operations.

Clinical product development involves a lengthy and expensive process, with uncertain outcomes. We may experience delays in completing, or ultimately be unable to complete, the development and commercialization of our current and future product candidates.

To obtain the requisite regulatory approvals to commercialize any of our product candidates, we must demonstrate through extensive preclinical studies and clinical trials that our products are safe or effective in humans. Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process and our future clinical trial results may not be successful.

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We may experience delays in completing our clinical trials or preclinical studies and initiating or completing additional clinical trials. We may also experience numerous unforeseen events during our clinical trials that could delay or prevent our ability to receive marketing approval or commercialize the product candidates we develop, including:

- regulators or Institutional Review Boards, or IRBs, or ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching, or fail to reach, agreement on acceptable terms with prospective trial sites and prospective contract research organizations, or CROs;
- the number of patients required for clinical trials may be larger than we anticipate;
- it may be difficult to enroll a sufficient number of patients with mutations in the signaling pathways our therapies are designed to target, or enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials or fail to return for post-treatment follow-up at a higher rate than we anticipate;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all, or may deviate from the clinical trial protocol or drop out of the trial, which may require that we add new clinical trial sites or investigators;
- the supply or quality of materials for product candidates we develop or other materials necessary to conduct clinical trials may be insufficient or inadequate; and
- our collaborators may delay the development process by waiting to take action or focusing on other priorities.

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

If we experience delays in the completion of, or termination of, any clinical trial of our product candidates, the commercial prospects of our product candidates will be harmed, and our ability to generate product revenues from any of these product candidates will be delayed. In addition, any delays in completing our clinical trials will increase our costs, slow down our product candidate development and approval process and jeopardize our ability to commence product sales and generate revenues. Significant clinical trial delays could also allow our competitors to bring products to market before we do or shorten any periods during which we have the exclusive right to commercialize our product candidates and impair our ability to commercialize our product candidates and may harm our business and results of operations.

All of our clinical trial sites for our RMC-4630 clinical studies are currently located in the U.S., and may be affected by the COVID-19 outbreak due to prioritization of hospital resources toward the COVID-19 outbreak, travel or quarantine restrictions imposed by federal, state or local governments, and the inability to access sites for initiation and patient monitoring and enrollment. As a result, patient screening, new patient

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enrollment, monitoring and data collection may be affected or delayed. We are aware of several clinical sites involved in our RMC-4630 clinical studies that have temporarily stopped or delayed enrolling new patients, with exemptions if appropriate. These developments may delay our clinical trial timelines. Some of our third-party manufacturers which we use for the supply of materials for product candidates or other materials necessary to manufacture product to conduct clinical trials are located in countries affected by COVID-19, and should they experience disruptions, such as temporary closures or suspension of services, we would likely experience delays in advancing these trials. Currently, we expect no material impact on the clinical supply of RMC-4630.

In addition, based on our own preclinical data and supported by observations by others, we are evaluating intermittent dosing schedules in our clinical program to allow us to maximize dose intensity and the depth of response. When dosed in clinical trials, this intermittent dosing approach may reduce patient compliance.

Any of these occurrences may harm our business, financial condition and prospects significantly. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates or result in the development of our product candidates being stopped early.

Historically, direct inhibition of any RAS protein itself has been challenging due to a lack of tractable, or “druggable,” binding pockets and we are not aware of any programs in clinical development that have successfully targeted any RAS(ON) protein. Given this approach is unproven, it may not be successful.

Historically, direct inhibition of any RAS protein has been challenging due to a lack of tractable, or “druggable,” binding pockets. Our tri-complex technology has enabled us to develop what we believe to be the first potent, selective cell-active inhibitors of multiple mutant RAS(ON) proteins. We are not aware of any programs in clinical development that have successfully targeted any RAS(ON) protein. We cannot be certain that our approach will lead to the development of approvable or marketable products, alone or in combination with other therapies.

The results of preclinical studies and early-stage clinical trials may not be predictive of future results.

The results of preclinical studies may not be predictive of the results of clinical trials, and the results of any early-stage clinical trials we commence may not be predictive of the results of the later-stage clinical trials. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy despite having progressed through preclinical studies and initial clinical trials. There can be no assurance that any of our current or future clinical trials will ultimately be successful or support further clinical development of any of our product candidates. There is a high failure rate for drugs proceeding through clinical trials. A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in clinical development even after achieving promising results in earlier studies. Even if our clinical trials are completed, the results may not be sufficient to obtain regulatory approval of any products. Any such setbacks in our clinical development could have a material adverse effect on our business and operating results.

Interim, “topline” and preliminary data from our clinical trials may differ materially from the final data.

From time to time, we may disclose interim data from our clinical trials. Interim data from clinical trials are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more data on existing patients become available. For example, we have reported interim Phase 1 clinical data for RMC-4630 as a single agent. As of the cutoff date of May 4, 2020, 87 patients had received treatment: 49 patients on a daily dosing schedule with a median exposure to study drug of only 1.8 months, and 38 patients on an intermittent dosing schedule, with median exposure to study drug of only 1.8 months. We have also reported interim Phase 1b/2 clinical data for RMC-4630 in combination with the MEK inhibitor cobimetinib. As of the cutoff date of November 14, 2019, these data included eight patients with median

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exposure to study drug of only 1.4 months. Our clinical trial program is ongoing, and the final results may be materially different from what we previously reported and what is reported in this prospectus. Adverse differences between interim data and final data could significantly harm our business, financial condition, results of operations and prospects. From time to time, we may also publicly disclose preliminary or “topline” data from our clinical trials, which are based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the topline results that we report may differ from future results of the same clinical trials, or different conclusions or considerations may qualify such topline results once additional data have been received and fully evaluated. Topline data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, topline data should be viewed with caution until the final data are available.

Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and the value of our company in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is typically a summary of extensive information, and you or others may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure, and any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise regarding a particular product, product candidate or our business. If the topline data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, our product candidates may be harmed, which could harm our business, financial condition, operating results and prospects.

If we encounter difficulties enrolling patients in our clinical trials, our clinical development activities could be delayed or otherwise be adversely affected.

The timely completion of clinical trials in accordance with their protocols depends, among other things, on our ability to enroll a sufficient number of patients who remain in the trial until its conclusion. We may experience difficulties in patient enrollment in our clinical trials for a variety of reasons. The enrollment of patients depends on many factors, including:

- the patient eligibility criteria defined in the protocol;
- our ability to enroll a sufficient number of patients with mutations in the signaling pathways our therapies are designed to target;
- the size of the patient population required for analysis of the trial's primary endpoints;
- the proximity of patients to study sites;
- the design of the trial;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience;
- clinicians' and patients' perceptions as to the potential advantages of the product candidate being studied in relation to other available therapies, including any new products that may be approved for the indications we are investigating;

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- our ability to obtain and maintain patient consents for participation in our clinical trials and, where appropriate, biopsies for future patient enrichment efforts;
- the risk that patients enrolled in clinical trials will not remain on the trial through the completion of evaluation; and
- the ability of our clinical trial investigators to enroll patients in cases of outbreak of disease, including COVID-19, or other natural disasters.

In addition, our clinical trials will compete with other clinical trials for product candidates that are in the same therapeutic areas (and that seek to evaluate patients with cancer cells having the same mutations, particularly with patients having KRAS^{G12C} mutations) as our current and potential future product candidates. This competition will reduce the number and types of patients available to us, because some patients who might have opted to enroll in our trials may instead opt to enroll in a trial conducted by one of our competitors. Since the number of qualified clinical investigators is limited, we conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our clinical trials at such sites. Moreover, because our current and potential future product candidates may represent a departure from more commonly used methods for cancer treatment, potential patients and their doctors may be inclined to use conventional therapies, such as chemotherapy, rather than enroll patients in our ongoing or any future clinical trials.

All of our clinical trial sites for our RMC-4630 clinical studies are currently located in the U.S., and may be affected by the COVID-19 outbreak due to prioritization of hospital resources toward the COVID-19 outbreak, travel or quarantine restrictions imposed by federal, state or local governments, and the inability to access sites for initiation and patient monitoring and enrollment. As a result, patient screening, new patient enrollment, monitoring and data collection may be affected or delayed. We are aware of several clinical sites involved in our RMC-4630 clinical studies that have temporarily stopped or delayed enrolling new patients, with exemptions if appropriate. These developments may delay our clinical trial timelines. Some of our third-party manufacturers which we use for the supply of materials for product candidates or other materials necessary to manufacture product to conduct clinical trials are located in countries affected by COVID-19, and should they experience disruptions, such as temporary closures or suspension of services, we would likely experience delays in advancing these trials. Currently, we expect no material impact on the clinical supply of RMC-4630.

Delays in patient enrollment may result in increased costs or may affect the timing or outcome of clinical trials, which could prevent completion of these trials and adversely affect our ability to advance the development of the product candidates we develop.

Our current or future product candidates may cause undesirable side effects or have other properties when used alone or in combination with other approved products or investigational new drugs that could delay or halt their clinical development, prevent their marketing approval, limit their commercial potential or result in significant negative consequences.

Undesirable or clinically unmanageable side effects could occur and cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities. Results of our trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics.

The RMC-4630-01 study is evaluating the safety, pharmacokinetics and pharmacodynamic effects of RMC-4630 as a single agent under daily and intermittent schedules. As of the cutoff date of May 4, 2020, for those receiving RMC-4630 on the intermittent dosing schedule, four patients (11%) had serious adverse events, or SAEs, thought to be possibly or probably related to the study drug as assessed by the trial sponsor across all

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intermittent dosing cohorts. Three SAEs were reported among three patients receiving 200 mg D1D4 (Grade 3 abdominal distention, Grade 3 anemia, Grade 2 deep vein thrombosis, one patient each). Four SAEs were reported in one patient receiving 240 mg D1D4 (pleural effusion, pulmonary embolism, nausea, and vomiting, all Grade 3). Three additional SAEs (cerebrovascular accident, multifocal pneumonia, and pleural effusion) were reported in which the investigator was unable to rule out an association with the study drug, but where the evidence for causality by RMC-4630 was absent or considered unlikely by the study sponsor. No treatment-related grade 4 or grade 5 adverse events, or AEs, had been reported as of the cutoff date. The most common treatment-related AEs for the intermittent dosing group were diarrhea (39.5%), anemia (26.3%), fatigue (26.3%), thrombocytopenia (26.3%) and edema (21.1%). For those receiving RMC-4630 on the daily schedule, three patients (6%) had SAEs thought to be possibly or probably related to the study drug as assessed by the trial sponsor. One Grade 2 event of dehydration was reported in the 60 mg daily cohort. One Grade 4 event of thrombocytopenia and one Grade 3 event of generalized edema were reported in the 80 mg daily cohort. Two additional SAEs (QTc prolongation and respiratory failure), both in the 60 mg daily cohort, were reported in which the investigator was unable to rule out an association with the study drug, but where the evidence for causality by RMC-4630 was absent or considered unlikely by the study sponsor. The most common treatment-related AEs for the daily dosing group were thrombocytopenia (30.6%), diarrhea (26.5%) and anemia (24.5%).

The RMC-4630-02 study is evaluating the safety, tolerability and pharmacokinetics of RMC-4630 and cobimetinib using intermittent dosing of RMC-4630 with daily dosing of cobimetinib. Alternative dosing schedules using intermittent dosing of one or both RMC-4630 and cobimetinib are also under evaluation. Adverse events were consistent with the expected mechanistic effects of both SHP2 inhibition and MEK inhibition. No SAEs or grade 4 or 5 AEs were reported in the RMC-4360-02 study as of the cutoff date of November 14, 2019. The most common AEs related to RMC-4630 were diarrhea (25.0%) and edema (25.0%). The most common AE related to cobimetinib was edema (25.0%).

Although our current and future product candidates will undergo safety testing to the extent possible and, where applicable, under such conditions discussed with regulatory authorities, not all adverse effects of drugs can be predicted or anticipated. Unforeseen side effects could arise either during clinical development or, if such side effects are more rare, after our products have been approved by regulatory authorities and the approved product has been marketed, resulting in the exposure of additional patients. So far, we have not previously demonstrated that RMC-4630 or any other product candidate is safe in humans, and we cannot predict if ongoing or future clinical trials will do so.

Furthermore, certain of our product candidates, such as RMC-4630, are currently being, and may in the future be, co-administered with approved or experimental therapies, such as Roche's cobimetinib, Amgen's sotorasib, a PD-1 inhibitor, or Lilly's LY-3214996. These combinations may have additional side effects. The uncertainty resulting from the use of our product candidates in combination with other therapies may make it difficult to accurately predict side effects in future clinical trials.

If any of our product candidates receives marketing approval and we or others later identify undesirable side effects caused by such products, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw their approval of the product;
- we may be required to recall a product or change the way such product is administered to patients;
- additional restrictions may be imposed on the marketing of the particular product or the manufacturing processes for the product or any component thereof;
- regulatory authorities may require the addition of labeling statements, such as a "black box" warning or a contraindication;

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- we may be required to implement a Risk Evaluation and Mitigation Strategy, or REMS, or create a Medication Guide outlining the risks of such side effects for distribution to patients;
- we could be sued and held liable for harm caused to patients;
- the product may become less competitive; and
- our reputation may suffer.

Any of the foregoing events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, and result in the loss of significant revenues to us, which would adversely affect our business, financial condition, results of operations and prospects. In addition, if one or more of our product candidates prove to be unsafe, our entire technology platform and pipeline could be affected, which would have a material adverse effect on our business, financial condition, results of operations and prospects.

Even if we complete the necessary preclinical studies and clinical trials, the marketing approval process is expensive, time-consuming and uncertain and may prevent us or any of our existing or future collaboration partners from obtaining approvals for the commercialization of RMC-4630 and any other product candidate we develop.

Any current or future product candidate we may develop and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale, and distribution, are subject to comprehensive regulation by the FDA and other regulatory authorities in the United States and by comparable authorities in other countries. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate in a given jurisdiction. We have not received approval to market any product candidates from regulatory authorities in any jurisdiction and it is possible that none of our current or future product candidates will ever obtain regulatory approval. We have no experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party CROs or regulatory consultants to assist us in this process. Securing regulatory approval requires the submission of extensive preclinical and clinical data and supporting information to the various regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing regulatory approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. Any product candidates we develop may not be effective, may be only moderately effective, or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive, may take many years if additional clinical trials are required, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity, and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. The FDA and comparable authorities in other countries have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit, or prevent marketing approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

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If we experience delays in obtaining approval or if we fail to obtain approval of any current or future product candidates we may develop, the commercial prospects for those product candidates may be harmed, and our ability to generate revenues will be materially impaired.

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

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

We may also submit marketing applications in other countries. Regulatory authorities in jurisdictions outside of the United States have requirements for approval of product candidates with which we must comply prior to marketing in those jurisdictions. Obtaining foreign marketing approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. If we fail to comply with the regulatory requirements in international markets and/or receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed.

Adverse events in the field of oncology could damage public perception of our current or future product candidates and negatively affect our business.

The commercial success of our products will depend in part on public acceptance of the use of targeted cancer therapies. While a number of targeted cancer therapies have received regulatory approval and are being commercialized, our approach to targeting cancer cells carrying tumor causing mutations, including oncogenic RAS(ON) pathway mutations, is novel and unproven. Adverse events in clinical trials of our product candidates, or post-marketing activities, or in clinical trials of others developing similar products and the resulting publicity, as well as any other adverse events in the field of oncology that may occur in the future, could result in a decrease in demand for any product that we may develop. If public perception is influenced by claims that the use of cancer therapies is unsafe, whether related to our therapies or those of our competitors, our products may not be accepted by the general public or the medical community.

Future adverse events in oncology or the biopharmaceutical industry could also result in greater governmental regulation, stricter labeling requirements and potential regulatory delays in the testing or approvals of our products. Any increased scrutiny could delay or increase the costs of obtaining marketing approval for the product candidates we develop.

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Even if we receive marketing approval of a product candidate, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our products, if approved.

Any marketing approvals that we receive for any current or future product candidate may be subject to limitations on the approved indicated uses for which the product may be marketed or the conditions of approval, or contain requirements for potentially costly post-market testing and surveillance to monitor the safety and efficacy of the product candidate. The FDA may also require REMS as a condition of approval of any product candidate, which could include requirements for a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. In addition, if the FDA or a comparable foreign regulatory authority approves a product candidate, the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion, import and export and record keeping for the product candidate will be subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with current Good Manufacturing Practice, or cGMP, and Good Clinical Practice, or GCP, for any clinical trials that we conduct post-approval. Later discovery of previously unknown problems with any approved candidate, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

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

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

Even if a current or future product candidate receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success.

If any current or future product candidate we develop receives marketing approval, whether as a single agent or in combination with other therapies, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors, and others in the medical community. For example, current approved immunotherapies, and other cancer treatments like chemotherapy and radiation therapy, are well established in the medical community, and doctors may continue to rely on these therapies. If the product candidates we develop do not achieve an adequate level of acceptance, we may not generate significant product revenues and

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we may not become profitable. The degree of market acceptance of any product candidate, if approved for commercial sale, will depend on a number of factors, including:

- efficacy and potential advantages compared to alternative treatments;
- the ability to offer our products, if approved, for sale at competitive prices;
- convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support;
- the ability to obtain sufficient third-party coverage and adequate reimbursement, including with respect to the use of the approved product as a combination therapy;
- adoption of a companion diagnostic and/or complementary diagnostic (if any); and
- the prevalence and severity of any side effects.

The market opportunities for any current or future product candidate we develop, if and when approved, may be limited to those patients who are ineligible for established therapies or for whom prior therapies have failed, and may be small.

Cancer therapies are sometimes characterized as first-line, second-line, or third-line, and the FDA often approves new therapies initially only for third-line use. When cancer is detected early enough, first-line therapy, usually chemotherapy, hormone therapy, surgery, radiation therapy or a combination of these, is sometimes adequate to cure the cancer or prolong life without a cure. Second- and third-line therapies are administered to patients when prior therapy is not effective. We expect to initially seek approval of RMC-4630 and any other product candidates we develop as a therapy for patients who have received one or more prior treatments. Subsequently, for those products that prove to be sufficiently beneficial, if any, we would expect to seek approval potentially as a first-line therapy, but there is no guarantee that product candidates we develop, even if approved, would be approved for first-line therapy, and, prior to any such approvals, we may have to conduct additional clinical trials.

The number of patients who have the cancers we are targeting may turn out to be lower than expected. Additionally, the potentially addressable patient population for our current programs or future product candidates may be limited, if and when approved. Even if we obtain significant market share for any product candidate, if and when approved, if the potential target populations are small, we may never achieve profitability without obtaining marketing approval for additional indications, including to be used as first- or second-line therapy.

We are developing RMC-4630 in combination with Roche's cobimetinib and with Amgen's sotorasib, and may in the future, develop RMC-4630 and other product candidates in combination with other therapies, which exposes us to additional risks.

We are developing RMC-4630 in combination with Roche's cobimetinib and with Amgen's sotorasib, and may in the future, develop RMC-4630 and other product candidates in combination with one or more currently approved cancer therapies. Even if any product candidate we develop were to receive marketing approval or be commercialized for use in combination with other existing therapies, we would continue to be subject to the risks that the FDA or similar regulatory authorities outside of the United States could revoke approval of the therapy used in combination with our product candidate or that safety, efficacy, manufacturing or supply issues

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could arise with these existing therapies. Combination therapies are commonly used for the treatment of cancer, and we would be subject to similar risks if we develop any of our product candidates for use in combination with other drugs or for indications other than cancer. This could result in our own products being removed from the market or being less successful commercially.

We may also evaluate RMC-4630 or any other current or future product candidates in combination with one or more other cancer therapies, such as Lilly's LY-3214996, that have not yet been approved for marketing by the FDA or similar regulatory authorities outside of the United States or with approved cancer therapies at an unapproved dose and/or schedule, and/or with approved cancer therapies in unapproved indications. We will not be able to market and sell RMC-4630 or any product candidate we develop in combination with any such cancer therapies outside existing approved labels that do not ultimately obtain marketing approval.

If the FDA or similar regulatory authorities outside of the United States do not approve these other drugs or revoke their approval of, or if safety, efficacy, manufacturing, or supply issues arise with, the drugs we choose to evaluate in combination with or any product candidate we develop, we may be unable to obtain approval of or market or any product candidate we develop.

In addition, Sanofi primarily controls the research and development activities of our SHP2 inhibitors, including RMC-4630, pursuant to the terms of the Sanofi Agreement, and may disagree with us regarding which other therapies should be evaluated in combination with RMC-4630. As a result of any such disagreement, our completion of a trial in combination with our preferred combination product candidate may be delayed or prevented. We rely on Sanofi for the supply of RMC-4630 for future combination studies and if Sanofi is unwilling to supply RMC-4630 to be used in combination with a product candidate from our pipeline, our ability to complete a trial evaluating such combination may be delayed or prevented.

We face significant competition, and if our competitors develop and market products that are more effective, safer or less expensive than the product candidates we develop, our commercial opportunities will be negatively impacted.

The life sciences industry is highly competitive. We are currently developing therapies that will compete, if approved, with other products and therapies that currently exist or are being developed. Products we may develop in the future are also likely to face competition from other products and therapies, some of which we may not currently be aware. We have competitors both in the United States and internationally, including major multinational pharmaceutical companies, established biotechnology companies, specialty pharmaceutical companies, universities and other research institutions. Many of our competitors have significantly greater financial, manufacturing, marketing, product development, technical and human resources than we do. Large pharmaceutical companies, in particular, have extensive experience in clinical testing, obtaining marketing approvals, recruiting patients and manufacturing pharmaceutical products. These companies also have significantly greater research and marketing capabilities than we do and may also have products that have been approved or are in late stages of development, and collaborative arrangements in our target markets with leading companies and research institutions. Established pharmaceutical companies may also invest heavily to accelerate discovery and development of novel compounds or to in-license novel compounds that could make the product candidates that we develop obsolete. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. As a result of all of these factors, our competitors may succeed in obtaining patent protection and/or marketing approval or discovering, developing and commercializing products in our field before we do.

There are a large number of companies developing or marketing treatments for cancer, including many major pharmaceutical and biotechnology companies. These treatments consist of small molecule drug products, biologics, cell-based therapies and traditional chemotherapy. There are also several programs in development

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targeting SHP2, including those clinical programs run by Novartis AG, Jacobio Pharmaceuticals Co. Ltd., and Relay Therapeutics Inc. There are several RAS pathway mutations programs, including those directed at KRAS^{G12C}(OFF) and KRAS^{G12D}(OFF) mutations, including clinical programs directed at KRAS^{G12C}(OFF) being conducted by Amgen Inc., Mirati Therapeutics, Inc., Johnson & Johnson, AstraZeneca plc and Eli Lilly & Co. Other clinical programs directed at mutant RAS are being conducted by Merck & Co./Moderna Therapeutics, Boehringer Ingelheim and Gilead Sciences, Inc.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe effects, are more convenient, have a broader label, are marketed more effectively, are reimbursed or are less expensive than any products that we may develop. Our competitors also may obtain FDA, EMA or other marketing approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. Even if the product candidates we develop achieve marketing approval, they may be priced at a significant premium over competitive products if any have been approved by then, resulting in reduced competitiveness.

Smaller and other early stage companies may also prove to be significant competitors. In addition, academic research departments and public and private research institutions may be conducting research on compounds that could prove to be competitive. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. In addition, the biopharmaceutical industry is characterized by rapid technological change. If we fail to stay at the forefront of technological change, we may be unable to compete effectively. Technological advances or products developed by our competitors may render our product candidates obsolete, less competitive or not economical.

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

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

Our ability to commercialize any product candidates, whether as a single agent or combination therapy, successfully also will depend in part on the extent to which coverage and reimbursement for these product candidates and related treatments will be available from government authorities, private health insurers and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. It is difficult to predict at this time what government authorities and third-party payors will decide with respect to coverage and reimbursement for our programs.

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular products and requiring substitutions of generic products and/or biosimilars. Increasingly, third-party

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payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for drugs. We cannot be sure that coverage will be available for any product candidate that we commercialize and, if coverage is available, the level of reimbursement. These third-party payors are also examining the cost-effectiveness of drugs in addition to their safety and efficacy.

Reimbursement may impact the demand for, or the price of, any product candidate for which we obtain marketing approval. If reimbursement is not available or is available only to limited levels, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval.

There may be significant delays in obtaining coverage and reimbursement for newly approved drugs, as the process is time-consuming and costly, and coverage may be more limited than the purposes for which the drug is approved by the FDA or comparable foreign regulatory authorities. Additionally, no uniform policy requirement for coverage and reimbursement for drug products exists among third-party payors in the United States, which may result in coverage and reimbursement for drug products that can differ significantly from payor to payor. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Our inability to promptly obtain coverage and profitable payment rates from both government-funded and private payors for any approved drugs that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize drugs and our overall financial condition.

We may fail to select or capitalize on the most scientifically, clinically and commercially promising or profitable mutant RAS(ON) target.

We have limited technical, managerial and financial resources to determine which of our lead generation stage RAS(ON) inhibitors should be advanced into further preclinical development, initial clinical trials, later-stage clinical development and potential commercialization. Initially, we are prioritizing four mutant RAS(ON) targets—KRAS^{G12C}, KRAS^{G13C}, KRAS^{G12D} and NRAS^{G12C}—and expect to nominate our first development candidate in 2020. In selecting a development candidate, we may make incorrect determinations. Our decisions to allocate our research and development, management and financial resources toward particular development candidates or therapeutic areas may not lead to the development of viable commercial products and may divert resources from better opportunities. Similarly, our decisions to delay or terminate development programs may also be incorrect and could cause us to miss valuable opportunities.

We may not be successful in our efforts to identify or discover other product candidates and may fail to capitalize on programs or product candidates that may present a greater commercial opportunity or for which there is a greater likelihood of success.

The success of our business depends upon our ability to identify, develop and commercialize product candidates. If we do not successfully develop and eventually commercialize products, we will face difficulty in obtaining product revenue in future periods, resulting in significant harm to our financial position and adversely affecting our share price. Research programs to identify new product candidates require substantial technical, financial and human resources, and we may fail to identify potential product candidates for numerous reasons.

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Additionally, because we have limited resources beyond those provided by Sanofi on SHP2 and RMC-4630, we may forego or delay pursuit of opportunities with certain programs or product candidates or for indications that later prove to have greater commercial potential. For example, we currently intend to focus on the development of RMC-4630. However, the advancement of this product candidate may ultimately prove to be unsuccessful or less successful than another program in our pipeline that we might have chosen to pursue on a less aggressive basis. Our estimates regarding the potential market for our product candidates could be inaccurate, and our spending on current and future research and development programs may not yield any commercially viable products. If we do not accurately evaluate the commercial potential for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. For example, we licensed worldwide development and commercialization rights with respect to RMC-4630 to Sanofi and will receive only milestone payments, an equal share of profits and losses in the United States and royalties on annual net sales of each product outside the United States. Alternatively, we may allocate internal resources to a product candidate in a therapeutic area in which it would have been more advantageous to enter into a partnering arrangement.

If any of these events occur, we may be forced to abandon or delay our development efforts with respect to a particular product candidate or fail to develop a potentially successful product candidate, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

We may need to use existing commercial diagnostic tests or develop, or enter into a collaboration or partnership to develop, novel complementary diagnostics and/or novel companion diagnostics for some of our current or future product candidates. If we or our future partners are unable to successfully develop such companion diagnostics or complementary diagnostics, or experience significant delays in doing so, we may not realize the full commercial potential of our future product candidates.

As one of the key elements of our product development strategy, we seek to identify cancer patient populations that may derive meaningful benefit from our current or future product candidates. Because predictive biomarkers may be used to identify the right patients for our programs and our current or future product candidates, we believe that our success may depend, in part, on our ability to use existing diagnostic tests (such as Foundation Medicine's FoundationOne® CDX), or develop novel complementary diagnostics and/or novel companion diagnostics in collaboration with partners.

In the event that novel tests will need to be developed, we have little experience in the development of diagnostics. As such, we expect to rely on future partners in developing appropriate diagnostics to pair with our current or future product candidates. We have not yet begun discussions with any potential partners with respect to the development of complementary diagnostics and/or companion diagnostics and may be unsuccessful in entering into collaborations for the development of companion diagnostics for our programs and our current or future product candidates.

Complementary diagnostics and/or companion diagnostics are subject to regulation by the FDA and similar regulatory authorities outside the United States as medical devices and require separate regulatory approval or clearance prior to commercialization. If we, our partners, or any third parties that we engage to assist us, are unable to successfully develop complementary diagnostics and/or companion diagnostics for our product candidates and any future product candidates, or experience delays in doing so:

- the development of our product candidates and any other future product candidates may be adversely affected if we are unable to appropriately select patients for enrollment in our clinical trials; and

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- we may not realize the full commercial potential of our product candidates and any other future product candidates that receive marketing approval if, among other reasons, we are unable to appropriately identify, or it takes us longer to identify, patients who are likely to benefit from therapy with our products, if approved.

If any of these events were to occur, our business would be harmed, possibly materially.

We may seek and fail to obtain fast track or breakthrough therapy designations for our current or future product candidates. If we are successful, these programs may not lead to a faster development or regulatory review process, and they do not guarantee we will receive approval for any product candidate. We may also seek to obtain accelerated approval for one or more of our product candidates but the FDA may disagree that we have met the requirements for such approval.

If a product is intended for the treatment of a serious or life-threatening condition and preclinical or clinical data demonstrate the potential to address an unmet medical need for this condition, the product sponsor may apply for fast track designation. The FDA has broad discretion whether or not to grant this designation, so even if we believe a particular product candidate is eligible for this designation, we cannot assure you that the FDA would decide to grant it. Even if we do receive fast track designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may rescind the fast track designation if it believes that the designation is no longer supported by data from our clinical development program.

We may also seek breakthrough therapy designation for any product candidate that we develop. A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over currently approved therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Like fast track designation, breakthrough therapy designation is within the discretion of the FDA. Accordingly, even if we believe a product candidate we develop meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of breakthrough therapy designation for a product candidate may not result in a faster development process, review or approval compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if a product candidate we develop qualifies as a breakthrough therapy, the FDA may later decide that the drug no longer meets the conditions for qualification and rescind the designation.

Drugs designated as fast track products or breakthrough therapies by the FDA are also eligible for accelerated approval if the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. As a condition of accelerated approval, the FDA will generally require the sponsor to perform adequate and well-controlled post-marketing clinical studies to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit. In addition, the FDA requires pre-approval of promotional materials for accelerated approval products, once approved. We cannot guarantee that the FDA will agree any of our product candidates has met the criteria to receive accelerated approval, which would require us to conduct additional clinical testing prior to seeking FDA approval. Even if any of our product candidates received approval through this pathway, the product may fail required post-approval confirmatory clinical trials, and we may be required to remove the product from the market or amend the product label in a way that adversely impacts its marketing.

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We may seek Orphan Drug Designation for product candidates we develop, and we may be unsuccessful or may be unable to maintain the benefits associated with Orphan Drug Designation, including the potential for market exclusivity.

As part of our business strategy, we may seek Orphan Drug Designation for any product candidates we develop, and we may be unsuccessful. Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a drug as an orphan drug if it is a drug intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals annually in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the United States, Orphan Drug Designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers.

Similarly, in Europe, the European Commission grants Orphan Drug Designation after receiving the opinion of the EMA Committee for Orphan Medicinal Products on an Orphan Drug Designation application. Orphan Drug Designation is intended to promote the development of drugs that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than 5 in 10,000 persons in Europe and for which no satisfactory method of diagnosis, prevention, or treatment has been authorized (or the product would be a significant benefit to those affected). Additionally, designation is granted for drugs intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in Europe would be sufficient to justify the necessary investment in developing the drug. In Europe, Orphan Drug Designation entitles a party to a number of incentives, such as protocol assistance and scientific advice specifically for designated orphan medicines, and potential fee reductions depending on the status of the sponsor.

Generally, if a drug with an Orphan Drug Designation subsequently receives the first marketing approval for the indication for which it has such designation, the drug is entitled to a period of marketing exclusivity, which precludes the EMA or the FDA from approving another marketing application for the same drug and indication for that time period, except in limited circumstances. The applicable period is seven years in the United States and ten years in Europe. The European exclusivity period can be reduced to six years if a drug no longer meets the criteria for Orphan Drug Designation or if the drug is sufficiently profitable such that market exclusivity is no longer justified.

Even if we obtain orphan drug exclusivity for a product candidate, that exclusivity may not effectively protect the product candidate from competition because different therapies can be approved for the same condition. Even after an orphan drug is approved, the FDA can subsequently approve the same drug for the same condition if the FDA concludes that the later drug is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. In addition, a designated orphan drug may not receive orphan drug exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation. Moreover, orphan drug exclusive marketing rights in the United States may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition. Orphan Drug Designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process. While we may seek Orphan Drug Designation for applicable indications for our current and any future product candidates, we may never receive such designations. Even if we do receive such designations, there is no guarantee that we will enjoy the benefits of those designations.

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If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of any approved products.

We face an inherent risk of product liability as a result of the clinical testing of product candidates and will face an even greater risk if we commercialize any products. For example, we may be sued if any product candidate we develop causes or is perceived to cause injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of any approved products. Even successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for any approved product;
- injury to our reputation;
- withdrawal of clinical trial participants;
- initiation of investigations by regulators;
- costs to defend the related litigation;
- a diversion of management's time and our resources;
- substantial monetary awards to trial participants or patients;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- exhaustion of any available insurance and our capital resources;
- the inability to commercialize any product candidate; and
- a decline in our share price.

Our inability to obtain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of products we develop, alone or with collaboration partners.

Insurance coverage is increasingly expensive. We may not be able to maintain insurance at a reasonable cost or in an amount adequate to satisfy any liability that may arise, if at all. Our insurance policy contains various exclusions, and we may be subject to a product liability claim for which we have no coverage. We may have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts. Even if our agreements with Sanofi or any future collaborator entitle us to indemnification against losses, such indemnification may not be available or adequate should any claim arise.

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

In the United States, there have been and continue to be a number of legislative initiatives to contain healthcare costs. For example, in March 2010, the Affordable Care Act, or the ACA, was passed, which

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substantially changes the way healthcare is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry. The ACA, among other things, increases the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extends the rebate program to individuals enrolled in Medicaid managed care organizations, establishes annual fees and taxes on manufacturers of certain branded prescription drugs, and creates a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 70% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D.

Some of the provisions of the ACA have yet to be fully implemented, while certain provisions have been subject to judicial and Congressional challenges, as well as efforts by the Trump administration to repeal or replace certain aspects of the ACA. By way of example, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. In addition, the Tax Cuts and Jobs Act, or the TCJA, includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." On December 14, 2018, a Texas U.S. District Court Judge ruled that the ACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the TCJA. On December 18, 2019, the U.S. Court of Appeals for the 5th Circuit ruled that the individual mandate was unconstitutional and remanded the case back to the District Court to determine whether the remaining provisions of the ACA are invalid as well. On March 2, 2020, the U.S. Supreme Court granted the petitions for writs of certiorari to review the case, although it is unclear when a decision will be made or how the Supreme Court will rule. In addition, there may be other efforts to challenge, repeal or replace the ACA.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. On August 2, 2011, the Budget Control Act of 2011, among other things, included aggregate reductions of Medicare payments to providers of 2% per fiscal year. These reductions went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2029 unless additional congressional action is taken. The Coronavirus Aid, Relief and Economic Security Act, or CARES Act, which was signed into law in March 2020 and is designed to provide financial support and resources to individuals and businesses affected by the COVID-19 pandemic, suspended the 2% Medicare sequester from May 1, 2020 through December 31, 2020, and extended the sequester by one year, through 2030. In addition, on January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers.

Moreover, payment methodologies may be subject to changes in healthcare legislation and regulatory initiatives. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for any product candidate we develop or complementary diagnostics or companion diagnostics or additional pricing pressures.

Additionally, there has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs.

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We are subject to certain U.S. and foreign anti-corruption, anti-money laundering, export control, sanctions, and other trade laws and regulations. We can face serious consequences for violations.

Among other matters, U.S. and foreign anti-corruption, anti-money laundering, export control, sanctions, and other trade laws and regulations, which are collectively referred to as Trade Laws, prohibit companies and their employees, agents, clinical research organizations, legal counsel, accountants, consultants, contractors, and other partners from authorizing, promising, offering, providing, soliciting, or receiving directly or indirectly, corrupt or improper payments or anything else of value to or from recipients in the public or private sector. Violations of Trade Laws can result in substantial criminal fines and civil penalties, imprisonment, the loss of trade privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm, and other consequences. We have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. We also expect our non-U.S. activities to increase in time. We plan to engage third parties for clinical trials and/or to obtain necessary permits, licenses, patent registrations, and other regulatory approvals and we can be held liable for the corrupt or other illegal activities of our personnel, agents, or partners, even if we do not explicitly authorize or have prior knowledge of such activities.

Risks related to reliance on third parties

We are dependent on our collaboration with Sanofi for the development of RMC-4630 and may depend on Sanofi for the development and commercialization of any other future SHP2 inhibitor product candidates. Under certain circumstances, Sanofi may unilaterally terminate the collaboration for convenience, which would materially and adversely affect our business.

In June 2018, we entered into a collaborative research, development and commercialization agreement with Sanofi, or the Sanofi Agreement, focused on researching, developing and commercializing SHP2 inhibitors as cancer therapies and potentially other indications. Sanofi primarily controls the research and development activities pursuant to the terms of the Sanofi Agreement, and our lack of control over such activities, including with respect to RMC-4630, could result in delays or other difficulties in the development and commercialization of product candidates, which may prevent completion of intended NDA filings in a timely fashion, if at all. Because of the allocation of responsibilities under the Sanofi Agreement, we are wholly dependent on Sanofi for the success of the RMC-4630 program. Any dispute with Sanofi may result in the delay or termination of the research, development or commercialization of RMC-4630 or other SHP2 inhibitor product candidates, and may result in costly litigation that diverts management attention and resources away from our day-to-day activities, which may adversely affect our business, financial condition, results of operation and prospects. For example, we plan to evaluate RMC-4630 in combination with other therapies (which may include product candidates from our pipeline), and Sanofi may disagree with us regarding which other therapies should be evaluated in combination with RMC-4630. As a result of this disagreement, our completion of a trial in combination with our preferred combination product candidate may be delayed or prevented. We rely on Sanofi for the supply of RMC-4630 for future combination studies and if Sanofi is unwilling to supply RMC-4630 to be used in combination with a product candidate from our pipeline, our ability to complete a trial evaluating such combination may be delayed or prevented.

In addition, Sanofi can terminate the Sanofi Agreement (including for convenience), and in the event Sanofi terminates the Sanofi Agreement, we would be prevented from receiving any research and development funding, milestone payments, profit share payments, royalty payments and other benefits under that agreement. Termination of the Sanofi Agreement could require us to seek additional funding in order to avoid delaying, reducing the scope of, or suspending, one or more of our research and development programs or clinical trials. In addition, any decision by Sanofi to terminate the Sanofi Agreement may negatively impact

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public perception of RMC-4630, or all of the SHP2 program covered by the Sanofi Agreement, which could adversely affect the market price of our common stock. We cannot provide any assurance with respect to the success of the Sanofi collaboration. Any of the foregoing events could have a materially adverse effect on our business, financial condition, results of operation and prospects. For more information regarding the Sanofi Agreement, see “Business—Collaboration agreement with Sanofi.”

In addition to our collaboration with Sanofi, we may depend on collaborations with other third parties for the development and commercialization of our product candidates in the future. If our collaborations are not successful, we may not be able to capitalize on the market potential of these product candidates.

In the future, we may form or seek other strategic alliances, joint ventures, or collaborations, or enter into additional licensing arrangements with third parties that we believe will complement or augment our development and commercialization efforts with respect to product candidates we develop.

Collaborations involving our current and future product candidates, including our current collaborations with Sanofi, Roche and Amgen may pose the following risks to us:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial, abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates;
- a collaborator with marketing, manufacturing and distribution rights to one or more products may not commit sufficient resources to or otherwise not perform satisfactorily in carrying out these activities;
- collaborators may not properly prosecute, maintain, enforce or defend our intellectual property rights or may use our proprietary information in a way that gives rise to actual or threatened litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation, or other intellectual property proceedings;
- collaborators may own or co-own intellectual property covering products that result from our collaboration with them, and in such cases, we may not have the exclusive right to develop, license or commercialize such intellectual property;
- disputes may arise with respect to ownership of any intellectual property developed pursuant to our collaborations;
- disputes may arise between a collaborator and us that cause the delay or termination of the research, development or commercialization of the product candidate, or that result in costly litigation or arbitration that diverts management attention and resources; and
- if a present or future collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program under such collaboration could be delayed, diminished or terminated.

As a result, if we enter into additional collaboration agreements and strategic partnerships or license our intellectual property, products or businesses, we may not be able to realize the benefit of such transactions if we are unable to successfully integrate them with our existing operations, which could delay our timelines or

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otherwise adversely affect our business. We also cannot be certain that, following a strategic transaction or license, we will achieve the revenue or specific net income that justifies such transaction. Any delays in entering into new collaborations or strategic partnership agreements related to any product candidate we develop could delay the development and commercialization of our product candidates, which would harm our business prospects, financial condition, and results of operations.

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

The advancement of our product candidates and development programs and the potential commercialization of our current and future product candidates will require substantial additional cash to fund expenses. For some of our programs, we may decide to collaborate with additional pharmaceutical and biotechnology companies with respect to development and potential commercialization. Any of these relationships may require us to incur non-recurring and other charges, increase our near and long term expenditures, issue securities that dilute our existing stockholders, or disrupt our management and business.

We face significant competition in seeking appropriate strategic partners and the negotiation process is time-consuming and complex. Whether we reach a definitive agreement for other collaborations will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the progress of our clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for our product candidate. Further, we may not be successful in our efforts to establish a strategic partnership or other alternative arrangements for future product candidates because they may be deemed to be at too early of a stage of development for collaborative effort and third parties may not view them as having the requisite potential to demonstrate safety and efficacy.

We may also be restricted under existing collaboration agreements from entering into future agreements on certain terms with potential collaborators. For example, under the Sanofi Agreement, we have granted worldwide exclusive rights under our intellectual property to Sanofi for SHP2 inhibitors, and during the term of the agreement we will be restricted from granting similar rights to other parties. This exclusivity could limit our ability to enter into collaborations with future collaborators.

In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

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

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If conflicts arise between us and our collaborators or strategic partners, these parties may act in a manner adverse to us and could limit our ability to implement our strategies.

If conflicts arise between our corporate or academic collaborators or strategic partners and us, the other party may act in a manner adverse to us and could limit our ability to implement our strategies. Sanofi or future collaborators or strategic partners may develop, either alone or with others, products in related fields that are competitive with the products or potential products that are the subject of these collaborations. Competing products, either developed by the collaborators or strategic partners or to which the collaborators or strategic partners have rights, may result in the withdrawal of partner support for our product candidates. Our current or future collaborators or strategic partners may preclude us from entering into collaborations with their competitors, fail to obtain timely regulatory approvals, terminate their agreements with us prematurely, or fail to devote sufficient resources to the development and commercialization of products. Any of these developments could harm our product development efforts.

We rely on third parties to conduct our ongoing and planned clinical trials for RMC-4630 and any other product candidates we develop. If these third parties do not successfully carry out their contractual duties, comply with regulatory requirements or meet expected deadlines, we may not be able to obtain marketing approval for or commercialize RMC-4630 and any other product candidates we develop and our business could be substantially harmed.

We do not have the ability to independently conduct clinical trials. We rely on medical institutions, clinical investigators, contract laboratories, and other third parties, including collaboration partners, to conduct or otherwise support clinical trials for RMC-4630 and other product candidates. We rely heavily on these parties for execution of clinical trials and control only certain aspects of their activities. Nevertheless, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, legal and regulatory requirements and scientific standards, and our reliance on CROs will not relieve us of our regulatory responsibilities. For any violations of laws and regulations during the conduct of our clinical trials, we could be subject to untitled and warning letters or enforcement action that may include civil penalties up to and including criminal prosecution.

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

Although we intend to design the clinical trials for our product candidates, or be involved in the design when other parties sponsor the trials, third parties conduct all of the clinical trials. For example, Amgen is conducting

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the Phase 1b trial evaluating the combination of RMC-4630 and sotorasib and Sanofi will conduct the planned Phase 1 trial evaluating the combination of RMC-4630 and a PD-1 inhibitor. In addition, in March 2020, the Pancreatic Cancer Collective (a strategic partnership between Lustgarten Foundation and Stand Up To Cancer) announced that it had awarded funding to the Netherlands Cancer Institute for its study using RMC-4630 in combination with an investigational ERK inhibitor (LY3214996) in patients with pancreatic cancer. We plan to provide RMC-4630 to support this investigator sponsored study. As a result, many important aspects of our clinical development, including their conduct and timing, will be outside of our direct control. Our reliance on third parties to conduct future clinical trials will also result in less direct control over the management of data developed through clinical trials than would be the case if we were relying entirely upon our own staff. Communicating with outside parties can also be challenging, potentially leading to mistakes as well as difficulties in coordinating activities. Outside parties may:

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

These factors may materially adversely affect the willingness or ability of third parties to conduct our clinical trials and may subject us to unexpected cost increases that are beyond our control. If the CROs do not perform clinical trials in a satisfactory manner, breach their obligations to us or fail to comply with regulatory requirements, the development, marketing approval and commercialization of our product candidates may be delayed, we may not be able to obtain marketing approval and commercialize our product candidates, or our development program may be materially and irreversibly harmed. If we are unable to rely on clinical data collected by our CROs, we could be required to repeat, extend the duration of, or increase the size of any clinical trials we conduct and this could significantly delay commercialization and require significantly greater expenditures.

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

All of our clinical trial sites for our RMC-4630 clinical studies are currently located in the U.S., and may be affected by the COVID-19 outbreak due to prioritization of hospital resources toward the COVID-19 outbreak, travel or quarantine restrictions imposed by federal, state or local governments, and the inability to access sites for initiation and patient monitoring and enrollment. As a result, patient screening, new patient enrollment, monitoring and data collection may be affected or delayed. We are aware of several clinical sites involved in our RMC-4630 clinical studies that have temporarily stopped or delayed enrolling new patients, with exemptions if appropriate. These developments may delay our clinical trial timelines.

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We rely on third parties to manufacture preclinical and clinical drug supplies, and we intend to rely on third parties to produce commercial supplies of any approved product which increases the risk that we will not have sufficient quantities of such product candidates or products or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

We do not own or operate manufacturing facilities for the production of preclinical, clinical or commercial supplies of the product candidates that we are developing or evaluating in our development programs. We have limited personnel with experience in drug manufacturing and lack the resources and the capabilities to manufacture any of our product candidates on a preclinical, clinical or commercial scale. We rely on third parties for supply of our preclinical and clinical drug supplies (including key starting and intermediate materials), and our strategy is to outsource all manufacturing of our product candidates and products to third parties, including Sanofi.

In order to conduct clinical trials of product candidates, we will need to have them manufactured in potentially large quantities. Our third-party manufacturers may be unable to successfully increase the manufacturing capacity for any of our clinical drug supplies (including key starting and intermediate materials) in a timely or cost-effective manner, or at all. In addition, quality issues may arise during scale-up activities and at any other time. For example, ongoing data on the stability of our product candidates may shorten the expiry of our product candidates and lead to clinical trial material supply shortages, and potentially clinical trial delays. If these third-party manufacturers are unable to successfully scale up the manufacture of our product candidates in sufficient quality and quantity, the development, testing and clinical trials of that product candidate may be delayed or infeasible, and regulatory approval or commercial launch of that product candidate may be delayed or not obtained, which could significantly harm our business.

Our use of new third-party manufacturers increases the risk of delays in production or insufficient supplies of our product candidates (and the key starting and intermediate materials for such product candidates) as we transfer our manufacturing technology to these manufacturers and as they gain experience manufacturing our product candidates (and the key starting and intermediate materials for such product candidates).

Even after a third-party manufacturer has gained significant experience in manufacturing our product candidates (or the key starting and intermediate materials for such product candidates) or even if we believe we have succeeded in optimizing the manufacturing process, there can be no assurance that such manufacturer will produce sufficient quantities of our product candidates (or the key starting and intermediate materials for such product candidates) in a timely manner or continuously over time, or at all.

We may be delayed if we need to change the manufacturing process used by a third party. Further, if we change an approved manufacturing process, then we may be delayed if the FDA or a comparable foreign authority needs to review the new manufacturing process before it may be used.

We do not currently have any agreements with third-party manufacturers for long-term commercial supply. In the future, we may be unable to enter into agreements with third-party manufacturers for commercial supplies of any product candidate that we develop, or may be unable to do so on acceptable terms. Even if we are able to establish and maintain arrangements with third-party manufacturers, reliance on third-party manufacturers entails risks, including:

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

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Third-party manufacturers may not be able to comply with cGMP requirements or similar regulatory requirements outside the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable requirements could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and/or criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates.

Our future product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP requirements particularly for the development of monoclonal antibodies, and that might be capable of manufacturing for us.

If the third parties that we engage to supply any materials or manufacture product for our preclinical tests and clinical trials should cease to continue to do so for any reason, we likely would experience delays in advancing these tests and trials while we identify and qualify replacement suppliers or manufacturers and we may be unable to obtain replacement supplies on terms that are favorable to us. In addition, if we are not able to obtain adequate supplies of our product candidates or the substances used to manufacture them, it will be more difficult for us to develop our product candidates and compete effectively.

Some of our third-party manufacturers which we use for the supply of materials for product candidates or other materials necessary to manufacture product to conduct clinical trials are located in countries affected by COVID-19, and should they experience disruptions, such as temporary closures or suspension of services, we would likely experience delays in advancing these trials. Currently, we expect no material impact on the clinical supply of RMC-4630.

Our current and anticipated future dependence upon others for the manufacture of our product candidates (or the key starting and intermediate materials for such product candidates) may adversely affect our future profit margins and our ability to develop product candidates and commercialize any products that receive marketing approval on a timely and competitive basis.

Our future relationships with customers and third-party payors in the United States and elsewhere may be subject, directly or indirectly, to applicable anti-kickback, fraud and abuse, false claims, transparency, health information privacy and security and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm, administrative burdens and diminished profits and future earnings.

Healthcare providers, physicians and third-party payors in the United States and elsewhere will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations, including, without limitation, the federal Anti-Kickback Statute and the federal False Claims Act, or FCA, which may constrain the business or financial arrangements and relationships through which we sell, market and distribute any products for which we obtain marketing approval. In addition, we may be subject to transparency laws and patient privacy regulation by the U.S. federal and state governments and by governments in foreign jurisdictions in which we conduct our business. The applicable federal, state and foreign healthcare laws and regulations that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe, or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual, or the purchase, lease, order or recommendation of any good, facility, item or service for which

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payment may be made, in whole or in part, under the Medicare and Medicaid programs or other federal healthcare programs. A person or entity can be found guilty of violating the statute without actual knowledge of the statute or specific intent to violate it. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers, and formulary managers on the other. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution;

- the federal civil and criminal false claims laws, including the FCA, and civil monetary penalty laws, which prohibit any person or entity from, among other things, knowingly presenting, or causing to be presented, a false, fictitious or fraudulent claim for payment to, or approval by, the federal government or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the FCA;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters. Similar to the federal Anti-Kickback Statute, a person or entity can be found guilty of violating HIPAA without actual knowledge of the statutes or specific intent to violate them;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their respective implementing regulations, which impose, among other things, specified requirements relating to the privacy, security and transmission of individually identifiable health information held by covered entities and their business associates. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions;
- the Physician Payments Sunshine Act, created under the ACA, and its implementing regulations, which requires manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to CMS information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Beginning in 2022, applicable manufacturers also will be required to report such information regarding payments and transfers of value provided, as well as ownership and investment interests held, during the previous year to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists and certified nurse midwives;
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers;
- analogous state laws and regulations, such as state anti-kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by

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non-governmental third-party payors, including private insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and healthcare and data protection laws in the European Union and other jurisdictions, including reporting requirements detailing interactions with and payments to healthcare providers and laws governing the privacy and security of certain protected information, such as the California Consumer Privacy Act, or CCPA, which creates individual privacy rights for California consumers and increases the privacy and security obligations of entities handling certain personal data, and General Data Protection Regulation, or GDPR, which imposes obligations and restrictions on the collection and use of personal data relating to individuals located in the European Economic Area, or the EEA, and the United Kingdom (including health data).

Because of the breadth of these laws and the narrowness of the statutory exceptions and regulatory safe harbors available under such laws, it is possible that some of our business activities could be subject to challenge under one or more of such laws. The scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform, especially in light of the lack of applicable precedent and regulations. Federal and state enforcement bodies have recently increased their scrutiny of interactions between healthcare companies and healthcare providers, which has led to a number of investigations, prosecutions, convictions and settlements in the healthcare industry. Ensuring that our business arrangements with third parties comply with applicable healthcare laws, as well as responding to investigations by government authorities, can be time- and resource-consuming and can divert management's attention from the business.

If our operations are found to be in violation of any of the laws described above or any other government regulations that apply to us, we may be subject to penalties, including civil, criminal and administrative penalties, damages, fines, disgorgement, individual imprisonment, possible exclusion from participation in federal and state funded healthcare programs, contractual damages and the curtailment or restricting of our operations, as well as additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws, any of which could harm our ability to operate our business and our financial results. Further, if the physicians or other providers or entities with whom we expect to do business are found not to be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs. In addition, the approval and commercialization of any product candidate we develop outside the United States will also likely subject us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws.

Risks related to intellectual property

If we and our collaborators are unable to obtain and maintain sufficient patent and other intellectual property protection for our product candidates and technology, our competitors could develop and commercialize products and technology similar or identical to ours, and we may not be able to compete effectively in our market or successfully commercialize any product candidates we may develop.

Our success depends in significant part on our ability and the ability of our collaborators to obtain, maintain, enforce and defend patents and other intellectual property rights with respect to our product candidates and technology and to operate our business without infringing, misappropriating, or otherwise violating the intellectual property rights of others. If we and our collaborators are unable to obtain and maintain sufficient

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intellectual property protection for RMC-4630 or other product candidates that we may identify, or if the scope of the intellectual property protection obtained is not sufficiently broad, our competitors and other third parties could develop and commercialize product candidates similar or identical to ours, and our ability (and the ability of our collaborators) to successfully commercialize RMC-4630 and other product candidates that we (and our collaborators) may pursue may be impaired. We have limited issued patents with respect to our SHP2 program, including RMC-4630, and we can provide no assurance that any of our current or future patent applications will result in issued patents or that any issued patents will provide us with any competitive advantage. Failure to obtain such issued patents could have a material adverse effect on our and Sanofi's ability to develop and commercialize SHP2 inhibitor products, including RMC-4630, and on our ability to receive milestone, royalty or other payments from Sanofi pursuant to the Sanofi Agreement.

We seek to protect our proprietary positions by, among other things, filing patent applications in the United States and abroad related to RMC-4630 or other product candidates that we may identify. Obtaining, maintaining, defending and enforcing pharmaceutical patents is costly, time consuming and complex, and we may not be able to file and prosecute all necessary or desirable patent applications, or maintain, enforce and license any patents that may issue from such patent applications, at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. We may not have the right to control the preparation, filing, prosecution and maintenance of patent applications, or to maintain the rights to patents licensed to or from third parties.

Although we enter into confidentiality agreements with parties who have access to confidential or patentable aspects of our research and development output, such as our employees, collaborators, CROs, contract manufacturers, consultants, advisors and other third parties, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. Further, we may not be aware of all third-party intellectual property rights potentially relating to our product candidates. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing or, in some cases, not at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions.

The patent position of pharmaceutical companies generally is highly uncertain, involves complex legal, technological and factual questions and has, in recent years, been the subject of much debate and litigation throughout the world. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States, or vice versa. As a result, the issuance, scope, validity, enforceability, and commercial value of our patent rights are highly uncertain. The subject matter claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Therefore, our pending and future patent applications may not result in patents being issued in relevant jurisdictions that protect our product candidates, in whole or in part, or which effectively prevent others from commercializing competitive product candidates, and even if our patent applications issue as patents in relevant jurisdictions, they may not issue in a form that will provide us with any meaningful protection for our product candidates or technology, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Additionally, our competitors may be able to circumvent our patents by developing similar or alternative product candidates or technologies in a non-infringing manner.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our patents may be challenged in the courts or patent offices in the United States and abroad. We may be subject to a third-party preissuance submission of prior art to the United States Patent and Trademark Office, or the USPTO, or become involved in opposition, derivation, revocation, reexamination, *inter partes* review, post-grant review or interference proceedings challenging our patent rights or the patent rights of others, or other

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proceedings in the USPTO or applicable foreign offices that challenge priority of invention or other features of patentability. An adverse determination in any such submission, proceeding or litigation could result in loss of exclusivity or freedom to operate, patent claims being narrowed, invalidated or held unenforceable, in whole or in part, limit the scope or duration of the patent protection of our product candidates, all of which could limit our ability to stop others from using or commercializing similar or identical product candidates or technology to compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, regardless of the outcome, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates, or could have a material adverse effect on our ability to raise funds necessary to continue our research programs or clinical trials. Such proceedings also may result in substantial cost and require significant time from our scientists and management, even if the eventual outcome is favorable to us.

In addition, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our patent portfolio may not provide us with sufficient rights to exclude others from commercializing products or technology similar or identical to ours for a meaningful amount of time, or at all. Moreover, some of our owned or licensed patents and patent applications are, and may in the future be, co-owned with third parties. If we are unable to obtain exclusive licenses to any such co-owners' interest in such patents or patent applications, such co-owners may be able to license their rights to other third parties, including our competitors, and our competitors could market competing products and technology. In addition, we may need the cooperation of any such co-owners in order to enforce such patents against third parties, and such cooperation may not be provided to us. Any of the foregoing could harm our competitive position, business, financial condition, results of operations and prospects.

We have entered into licensing agreements with third parties. If we fail to comply with our obligations in the agreements under which we license intellectual property rights to or from third parties, or these agreements are terminated, or we otherwise experience disruptions to our business relationships with our licensors or licensees, our competitive position, business, financial condition, results of operations and prospects could be harmed.

In addition to patent and other intellectual property rights we own or co-own, we have licensed, and may in the future license, patent and other intellectual property rights to and from other parties. Licenses may not provide us with exclusive rights to use the applicable intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our products and technology in the future. As a result, we may not be able to prevent competitors from developing and commercializing competitive products or technologies.

In addition, in some circumstances, we may not have the right to control the preparation, filing and prosecution of patent applications or to maintain, defend and enforce the patents that we license to or from third parties, and we may have to rely on our partners to fulfill these responsibilities. For example, in June 2018, we entered into the Sanofi Agreement, wherein we exclusively licensed the worldwide rights in our SHP2 inhibitor program, including RMC-4630, to Sanofi. Although we have review and comment rights regarding patent prosecution decisions, Sanofi retains ultimate decision-making control, as well as the sole and exclusive right to enforce infringement of or defend claims against patents that relate to SHP2 inhibitor products licensed to it pursuant to the Sanofi Agreement. Consequently, any such licensed patents and applications may not be prepared, filed, prosecuted, maintained, enforced, and defended in a manner consistent with the best interests of our business. If our current or future licensors, licensees or collaborators fail to prepare, file, prosecute, maintain, enforce, and defend licensed patents and other intellectual property rights, such rights may be reduced or eliminated, and our right to develop and commercialize any of our product candidates or technology that are the subject of

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such licensed rights could be adversely affected. In addition, our licensors may own or control intellectual property that has not been licensed to us and, as a result, we may be subject to claims, regardless of their merit, that we are infringing or otherwise violating the licensor's rights.

If we fail to comply with our obligations in the agreements under which we license intellectual property rights from third parties, the licensor may have the right to terminate the license. If these agreements are terminated, the underlying patents fail to provide the intended exclusivity or we otherwise experience disruptions to our business relationships with our licensors, we could lose intellectual property rights that are important to our business or be prevented from developing and commercializing our product candidates, and competitors could have the freedom to seek regulatory approval of, and to market, products identical to ours. Termination of these agreements or reduction or elimination of our rights under these agreements may also result in our having to negotiate new or reinstated agreements with less favorable terms, cause us to lose our rights under these agreements, including our rights to important intellectual property or technology, or impede, delay or prohibit the further development or commercialization of one or more product candidates that rely on such agreements. It is possible that we may be unable to obtain any additional licenses at a reasonable cost or on reasonable terms, if at all. In that event, we may be required to expend significant time and resources to redesign our product candidates or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis.

In addition, the research resulting in certain of our owned and in-licensed patent rights and technology was funded in part by the U.S. federal or state governments. As a result, the government may have certain rights, including march-in rights, to such patent rights and technology. When new technologies are developed with government funding, the government generally obtains certain rights in any resulting patents, including a non-exclusive license authorizing the government to use the invention for noncommercial purposes. These rights may permit the government to disclose our confidential information to third parties or allow third parties to use our licensed technology. The government can exercise its march-in rights if it determines that action is necessary because we fail to achieve practical application of the government-funded technology, because action is necessary to alleviate health or safety needs, to meet requirements of federal regulations, or to give preference to U.S. industry. In addition, our rights in such inventions may be subject to certain requirements to manufacture products embodying such inventions in the United States. Any of the foregoing could harm our competitive position, business, financial condition, results of operations and prospects.

Licensing of intellectual property is of critical importance to our business and involves complex legal, business and scientific issues and certain provisions in intellectual property license agreements may be susceptible to multiple interpretations. Disputes may arise between us and our licensing partners regarding intellectual property subject to a license agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- whether and the extent to which technology and processes of one party infringe on intellectual property of the other party that are not subject to the licensing agreement;
- rights to sublicense patent and other rights to third parties;
- any diligence obligations with respect to the use of the licensed technology in relation to development and commercialization of our product candidates, and what activities satisfy those diligence obligations;
- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property;
- rights to transfer or assign the license; and
- the effects of termination.

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The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could harm our business, financial condition, results of operations and prospects. Moreover, if disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates.

In addition, if our licensors fail to abide by the terms of the license, if the licensors fail to prevent infringement by third parties or if the licensed patents or other rights are found to be invalid or unenforceable, our business, competitive position, financial condition, results of operations and prospects could be materially harmed. For more information regarding our license agreements, see “Business—Collaboration agreement with Sanofi.” Any of the foregoing could harm our competitive position, business, financial condition, results of operations and prospects.

If we are unable to obtain licenses from third parties on commercially reasonable terms or at all, our business could be harmed.

It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our products, in which case we would be required to obtain a license from these third parties. The licensing of third-party intellectual property rights is a competitive area, and more established companies may pursue strategies to license or acquire third-party intellectual property rights that we may consider attractive or necessary. More established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third party intellectual property rights on terms that would allow us to make an appropriate return on our investment or at all. If we are unable to license such technology, or if we are forced to license such technology on unfavorable terms, our business could be materially harmed. If we are unable to obtain a necessary license, we may be unable to develop or commercialize the affected product candidates, which could materially harm our business, and the third parties owning such intellectual property rights could seek either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties or other forms of compensation. Even if we are able to obtain a license, it may be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. Any of the foregoing could harm our competitive position, business, financial condition, results of operations and prospects.

We may not identify relevant third-party patents or may incorrectly interpret the relevance, scope or expiration of a third-party patent, which might subject us to infringement claims or adversely affect our ability to develop and market our product candidates.

We cannot guarantee that any of our or our licensors’ patent searches or analyses, including the identification of relevant patents, the scope of patent claims or the expiration of relevant patents, are complete or thorough, nor can we be certain that we have identified each and every third-party patent and pending patent application in the United States and abroad that is relevant to or necessary for the commercialization of our product candidates in any jurisdiction. For example, U.S. patent applications filed before November 29, 2000 and certain U.S. patent applications filed after that date that will not be filed outside the United States remain confidential until patents issue. As mentioned above, patent applications in the United States and elsewhere are published approximately 18 months after the earliest filing for which priority is claimed, with such earliest filing date being commonly referred to as the priority date. Therefore, patent applications covering our product candidates could have been filed by third parties without our knowledge. Additionally, pending patent applications that have been published can, subject to certain limitations, be later amended in a manner that could cover our product candidates or the use of our product candidates. The scope of a patent claim is

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determined by an interpretation of the law, the written disclosure in a patent and the patent's prosecution history. Our interpretation of the relevance or the scope of a patent or a pending application may be incorrect, which may negatively impact our ability to market our product candidates. We may incorrectly determine that our product candidates are not covered by a third-party patent or may incorrectly predict whether a third party's pending application will issue with claims of relevant scope. Our determination of the expiration date of any patent in the United States or abroad that we consider relevant may be incorrect, which may negatively impact our ability to develop and market our product candidates. Our failure to identify and correctly interpret relevant patents may negatively impact our ability to develop and market our product candidates.

If we fail to identify and correctly interpret relevant patents, we may be subject to infringement claims. We cannot guarantee that we will be able to successfully settle or otherwise resolve such infringement claims. If we fail in any such dispute, in addition to being forced to pay damages, which may be significant, we may be temporarily or permanently prohibited from commercializing any of our product candidates that are held to be infringing. We might, if possible, also be forced to redesign product candidates so that we no longer infringe the third-party intellectual property rights. Any of these events, even if we were ultimately to prevail, could require us to divert substantial financial and management resources that we would otherwise be able to devote to our business and could adversely affect our business, financial condition, results of operations and prospects.

Patent terms may be inadequate to protect our competitive position on our product candidates for an adequate amount of time.

Patents have a limited lifespan. In the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional filing date. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired for a product candidate, we may be open to competition from competitive medications, including generic medications. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such product candidates might expire before or shortly after such product candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing product candidates similar or identical to ours for a meaningful amount of time, or at all.

Depending upon the timing, duration and conditions of any FDA marketing approval of our product candidates, one or more of our owned or licensed U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments, and similar legislation in the European Union and certain other countries. The Hatch-Waxman Amendments permit a patent term extension of up to five years for a patent covering an approved product as compensation for effective patent term lost during product development and the FDA regulatory review process. However, we may not receive an extension if we fail to exercise due diligence during the testing phase or regulatory review process, fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Moreover, the length of the extension could be less than we request. Only one patent per approved product can be extended, the extension cannot extend the total patent term beyond 14 years from approval and only those claims covering the approved drug, a method for using it or a method for manufacturing it may be extended. If we are unable to obtain patent term extension or the term of any such extension is less than we request, the period during which we can enforce our patent rights for the applicable product candidate will be shortened and our competitors may obtain approval to market competing products sooner. As a result, our revenue from applicable products could be reduced. Further, if this occurs, our competitors may take advantage of our investment in development and trials by referencing our clinical and preclinical data and launch their product earlier than might otherwise be the case, and our competitive position, business, financial condition, results of operations and prospects could be materially harmed.

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

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

Filing, prosecuting, maintaining, defending and enforcing patents on our product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and may export otherwise infringing products to territories where we have patent protection, but enforcement rights are not as strong as those in the United States. These products may compete with our product candidates and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of some countries do not favor the enforcement or protection of patents, trade secrets and other intellectual property, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our intellectual property and proprietary rights generally. Proceedings to enforce our intellectual property rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful.

Many foreign countries, including some European Union countries, India, Japan and China, have compulsory licensing laws under which a patent owner may be compelled under specified circumstances to grant licenses to third parties. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In those countries, we may have limited remedies if patents are infringed or if we are compelled to grant a license to a third party, which could materially diminish the value of the applicable patents. This could limit our potential revenue opportunities. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license, which could adversely affect our business, financial condition, results of operations and prospects.

Changes in patent law could diminish the value of patents in general, thereby impairing our ability to protect our product candidates.

Obtaining and enforcing patents in the pharmaceutical industry is inherently uncertain, due in part to ongoing changes in the patent laws. For example, in the United States, depending on decisions by Congress, the federal

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courts, and the USPTO, the laws and regulations governing patents, and interpretation thereof, could change in unpredictable ways that could weaken our and our licensors' or collaborators' ability to obtain new patents or to enforce existing or future patents. For example, the U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. Therefore, there is increased uncertainty with regard to our and our licensors' or collaborators' ability to obtain patents in the future, as well as uncertainty with respect to the value of patents once obtained.

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our and our licensors' or collaborators' patent applications and the enforcement or defense of our or our licensors' or collaborators' issued patents. For example, assuming that other requirements for patentability are met, prior to March 2013, in the United States, the first to invent the claimed invention was entitled to the patent, while outside the United States, the first to file a patent application was entitled to the patent. After March 2013, under the Leahy-Smith America Invents Act, or the Leahy-Smith Act, enacted in September 2011, the United States transitioned to a first inventor to file system in which, assuming that other requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent on an invention regardless of whether a third party was the first to invent the claimed invention. The Leahy-Smith Act also includes a number of significant changes that affect the way patent applications are prosecuted and may also affect patent litigation. These include allowing third-party submission of prior art to the USPTO during patent prosecution and additional procedures to challenge the validity of a patent by USPTO-administered post-grant proceedings, including post-grant review, *inter partes* review and derivation proceedings. The USPTO recently developed new regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, particularly the first inventor-to-file provisions. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our or our licensors' patent applications and the enforcement or defense of our or our licensors' issued patents. Similarly, statutory or judicial changes to the patent laws of other countries may increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. All of the foregoing could harm our business, financial condition, results of operations and prospects.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated if we fail to comply with these requirements.

Periodic maintenance fees, renewal fees, annuity fees, and various other fees are required to be paid to the USPTO and foreign patent agencies in several stages over the lifetime of a patent. In certain circumstances, we rely on our licensors and collaborators to pay these fees. The USPTO and various foreign patent agencies also require compliance with a number of procedural, documentary, fee payment and other similar requirements during the patent application and prosecution process. Non-compliance events that could result in abandonment or lapse of a patent or patent application include failure to respond to official communications within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. While an inadvertent lapse can in some cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which non-compliance can result in irrevocable abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. If we or our licensors or collaborators fail to maintain the patents and patent applications covering our product candidates, our competitors might be able to enter the market with similar or identical products or technology, which would harm our business, financial condition, results of operations and prospects.

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We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time-consuming and unsuccessful, and issued patents covering our technology and product candidates could be found invalid or unenforceable if challenged.

Competitors and other third parties may infringe or otherwise violate our issued patents or other intellectual property or the patents or other intellectual property of our licensors. In addition, our patents or the patents of our licensors may become involved in inventorship or priority disputes. Our pending patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until a patent issues from such applications. To counter infringement or other unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. Our ability to enforce patent rights also depends on our ability to detect infringement. It may be difficult to detect infringers who do not advertise the components or methods that are used in connection with their products and services. Moreover, it may be difficult or impossible to obtain evidence of infringement in a competitor's or potential competitor's product or service. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents or that our patents are invalid or unenforceable. In a patent infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, in whole or in part, construe the patent's claims narrowly or refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology. An adverse result in any litigation proceeding could put one or more of our owned or licensed patents at risk of being invalidated, held unenforceable or interpreted narrowly. We may find it impractical or undesirable to enforce our intellectual property against some third parties.

If we were to initiate legal proceedings against a third party to enforce a patent directed to our product candidates, or one of our future product candidates, the defendant could counterclaim that our patent is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, non-enablement or insufficient written description. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO or made a misleading statement during prosecution. Third parties may also raise similar claims before the USPTO or an equivalent foreign body, even outside the context of litigation. Potential proceedings include re-examination, post-grant review, inter partes review, interference proceedings, derivation proceedings and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). Such proceedings could result in the revocation of, cancellation of, or amendment to our patents in such a way that they no longer cover our technology or any product candidates that we may develop. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of the patent protection on the applicable product candidates or technology covered by the patent rendered invalid or unenforceable. Such a loss of patent protection would materially harm our business, financial condition, results of operations and prospects.

Interference proceedings provoked by third parties or brought by us or declared by the USPTO may be necessary to determine the priority of inventions with respect to our patents or patent applications. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be materially harmed if the prevailing party does not offer us a license on commercially reasonable terms.

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Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.

Some of our competitors are larger than we are and have substantially greater resources. They are, therefore, likely to be able to sustain the costs of complex patent litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Accordingly, despite our efforts, we may not be able to prevent third parties from infringing upon, misappropriating or otherwise violating our intellectual property. Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims could result in substantial costs and diversion of management resources, which could harm our business. In addition, the uncertainties associated with litigation could compromise our ability to raise the funds necessary to continue our clinical trials, continue our internal research programs, or in-license needed technology or other product candidates. There could also be public announcements of the results of the hearing, motions, or other interim proceedings or developments. If securities analysts or investors perceive those results to be negative, it could cause the price of shares of our common stock to decline. Any of the foregoing events could harm our business, financial condition, results of operation and prospects.

Third parties may initiate legal proceedings alleging that we are infringing, misappropriating or otherwise violating their intellectual property rights, the outcome of which would be uncertain and could negatively impact the success of our business.

Our commercial success depends upon our ability to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing, misappropriating or otherwise violating the intellectual property and other proprietary rights of third parties. There is considerable intellectual property litigation in the pharmaceutical industry. We may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our product candidates and their manufacture and our other technology, including re-examination, interference, post-grant review, inter partes review or derivation proceedings before the USPTO or an equivalent foreign body. Numerous U.S. and foreign issued patents and pending patent applications owned by third parties exist in the fields in which we are developing our product candidates. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future, regardless of their merit.

Even if we believe third-party intellectual property claims are without merit, there is no assurance that a court would find in our favor on questions of infringement, validity, enforceability or priority. A court of competent jurisdiction could hold that third-party patents asserted against us are valid, enforceable and infringed, which could materially and adversely affect our ability to commercialize any product candidates we may develop and any other product candidates or technologies covered by the asserted third-party patents. In order to successfully challenge the validity of any such U.S. patent in federal court, we would need to overcome a presumption of validity. As this burden is a high one requiring us to present clear and convincing evidence as to the invalidity of any such U.S. patent claim, there is no assurance that a court of competent jurisdiction would invalidate the claims of any such U.S. patent. If we are found to infringe, misappropriate or otherwise violate a third party's intellectual property rights, and we are unsuccessful in demonstrating that such rights are invalid or unenforceable, we could be required to obtain a license from such a third party in order to continue developing and marketing our products and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. We could be forced, including by court order, to cease commercializing the infringing technology or product. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations. In the event of a successful claim of infringement against us, we may have to pay

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substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties and other fees, redesign our infringing product candidate or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business. Any of the foregoing events would harm our business, financial condition, results of operations and prospects.

We may be subject to claims by third parties asserting that we or our employees have infringed upon, misappropriated or otherwise violated their intellectual property rights, or claiming ownership of what we regard as our own intellectual property.

Many of our employees were previously employed at other biotechnology or pharmaceutical companies. Although we try to ensure that our employees, consultants and advisors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these individuals have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's former employer. We may also be subject to claims that patents and applications we have filed to protect inventions of our employees, consultants and advisors, even those related to one or more of our product candidates, are rightfully owned by their former or concurrent employer. Litigation may be necessary to defend against these claims.

If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs, delay development of our product candidates and be a distraction to management. Any of the foregoing events would harm our business, financial condition, results of operations and prospects.

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

We or our licensors may be subject to claims that former employees, collaborators or other third parties have an interest in our owned or in-licensed patents, trade secrets, or other intellectual property as an inventor or co-inventor. For example, we or our licensors may have inventorship disputes arise from conflicting obligations of employees, consultants or others who are involved in developing our product candidates. While it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own. Our and their assignment agreements may not be self-executing or may be breached, and litigation may be necessary to defend against these and other claims challenging inventorship or our or our licensors' ownership of our owned or in-licensed patents, trade secrets or other intellectual property. If we or our licensors fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, intellectual property that is important to our product candidates. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

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

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be

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negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. As noted above, some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could compromise our ability to compete in the marketplace, including compromising our ability to raise the funds necessary to continue our clinical trials, continue our research programs, license necessary technology from third parties, or enter into development collaborations that would help us commercialize our product candidates, if approved. Any of the foregoing events would harm our business, financial condition, results of operations and prospects.

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

We rely on trade secrets and confidentiality agreements to protect our unpatented know-how, technology and other proprietary information (including unpatented know-how associated with Warp Drive) and to maintain our competitive position. Trade secrets and know-how can be difficult to protect. We seek to protect these trade secrets and other proprietary technology, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, collaborators, CROs, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. We cannot guarantee that we have entered into such agreements with each party that may have or has had access to our trade secrets or proprietary technology and processes. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Unauthorized parties may also attempt to copy or reverse engineer certain aspects of our products that we consider proprietary. Monitoring unauthorized uses and disclosures is difficult, and we do not know whether the steps we have taken to protect our proprietary information will be effective.

We also seek to preserve the integrity and confidentiality of our confidential proprietary information by maintaining physical security of our premises and physical and electronic security of our information technology systems, but it is possible that these security measures could be breached. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third party, our competitive position would be materially and adversely harmed.

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

Our registered or unregistered trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential collaborators or customers in our markets of interest. At times, competitors may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other trademarks or trademarks that incorporate variations of our registered or unregistered trademarks or trade names. Over

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the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be adversely affected. We may license our trademarks and trade names to third parties, such as distributors. Though these license agreements may provide guidelines for how our trademarks and trade names may be used, a breach of these agreements or misuse of our trademarks and tradenames by our licensees may jeopardize our rights in or diminish the goodwill associated with our trademarks and trade names. Our efforts to enforce or protect our proprietary rights related to trademarks, trade names, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely affect our business, financial condition, results of operations and prospects.

Intellectual property rights do not necessarily address all potential threats.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations and may not adequately protect our business or permit us to maintain our competitive advantage. For example:

- others may be able to make products that are similar to any product candidates we may develop or utilize similar technology but that are not covered by the claims of the patents that we license or may own in the future;
- we, or our current or future licensors might not have been the first to make the inventions covered by the issued patent or pending patent application that we license or may own in the future;
- we, or our current or future licensors might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our owned or licensed intellectual property rights;
- it is possible that our pending owned or licensed patent applications or those that we may own or license in the future will not lead to issued patents;
- issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- the patents of others may harm our business; and
- we may choose not to file a patent in order to maintain certain trade secrets or know-how, and a third party may subsequently file a patent covering such intellectual property.

Should any of these events occur, they could harm our business, financial condition, results of operations and prospects.

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

We are highly dependent on our key personnel, and if we are not successful in attracting, motivating and retaining highly qualified personnel, we may not be able to successfully implement our business strategy.

We are highly dependent on members of our executive team. The loss of the services of any of them may adversely impact the achievement of our objectives. Any of our executive officers could leave our employment at any time, as all of our employees are “at-will” employees. We currently do not have “key person” insurance on any of our employees. The loss of the services of one or more of our key personnel might impede the achievement of our research, development and commercialization objectives.

Recruiting and retaining qualified employees, consultants and advisors for our business, including scientific and technical personnel, also will be critical to our success. Competition for skilled personnel is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies and academic institutions for skilled individuals. In addition, failure to succeed in preclinical studies, clinical trials or applications for marketing approval may make it more challenging to recruit and retain qualified personnel. The inability to recruit, or the loss of services of certain executives, key employees, consultants or advisors, may impede the progress of our research, development and commercialization objectives and have a material adverse effect on our business, financial condition, results of operations and prospects.

We currently have no sales organization. If we are unable to establish sales capabilities on our own or through third parties, we may not be able to market and sell any products effectively, if approved, or generate product revenue.

We currently do not have a marketing or sales organization. In order to commercialize any product, if approved, in the United States and foreign jurisdictions, we must build our marketing, sales, distribution, managerial and other non-technical capabilities or make arrangements with third parties to perform these services, and we may not be successful in doing so. In advance of any of our product candidates receiving regulatory approval, we expect to establish a sales organization with technical expertise and supporting distribution capabilities to commercialize each such product candidate, which will be expensive and time-consuming. We have no prior experience in the marketing, sale and distribution of pharmaceutical products, and there are significant risks involved in building and managing a sales organization, including our ability to hire, retain, and incentivize qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel, and effectively manage a geographically dispersed sales and marketing team. Any failure or delay in the development of our internal sales, marketing and distribution capabilities would adversely impact the commercialization of these products. We may choose to collaborate with third parties that have direct sales forces and established distribution systems, either to augment our own sales force and distribution systems or in lieu of our own sales force and distribution systems. If we are unable to enter into such arrangements on acceptable terms or at all, we may not be able to successfully commercialize our product candidates. If we are not successful in commercializing products, either on our own or through arrangements with one or more third parties, we may not be able to generate any future product revenue and we would incur significant additional losses.

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

As of March 31, 2020, we had 100 full-time employees, including 84 employees engaged in research and development. As our development and commercialization plans and strategies develop, and as we transition into operating as a public company, we expect to need additional managerial, operational, sales, marketing,

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financial and other personnel. Future growth would impose significant added responsibilities on members of management, including:

- identifying, recruiting, integrating, maintaining and motivating additional employees;
- managing our internal development efforts effectively, including the clinical and FDA review process for RMC-4630 and any other product candidate we develop, while complying with our contractual obligations to contractors and other third parties; and
- improving our operational, financial and management controls, reporting systems and procedures.

Our future financial performance and our ability to advance development of and, if approved, commercialize RMC-4630 and any other product candidate we develop will depend, in part, on our ability to effectively manage any future growth, and our management may also have to divert a disproportionate amount of its attention away from day-to-day activities in order to devote a substantial amount of time to managing these growth activities.

We currently rely, and for the foreseeable future will continue to rely, in substantial part on certain independent organizations, advisors and consultants to provide certain services, including substantially all aspects of marketing approval, clinical management, and manufacturing. We cannot assure you that the services of independent organizations, advisors and consultants will continue to be available to us on a timely basis when needed, or that we can find qualified replacements. In addition, if we are unable to effectively manage our outsourced activities or if the quality or accuracy of the services provided by consultants is compromised for any reason, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain marketing approval of any current or future product candidates or otherwise advance our business. We cannot assure you that we will be able to manage our existing consultants or find other competent outside contractors and consultants on economically reasonable terms, or at all.

If we are not able to effectively expand our organization by hiring new employees and expanding our groups of consultants and contractors, we may not be able to successfully implement the tasks necessary to further develop and commercialize RMC-4630 and any future product candidates we develop and, accordingly, may not achieve our research, development and commercialization goals.

We have in the past engaged and may in the future engage in strategic transactions; such transactions could affect our liquidity, dilute our existing stockholders, increase our expenses and present significant challenges in focus and energy to our management or prove not to be successful.

From time to time, we may consider strategic transactions, such as acquisitions of companies, asset purchases and out-licensing or in-licensing of intellectual property, products or technologies. For example, in October 2018, we acquired all of the outstanding shares of Warp Drive Bio, which became our direct wholly-owned subsidiary.

Additional potential transactions that we may consider in the future include a variety of business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and investments. Any future transactions could result in potentially dilutive issuances of our equity securities, including our common stock, or the incurrence of debt, contingent liabilities, amortization expenses or acquired in-process research and development expenses, any of which could affect our financial condition, liquidity and results of operations. Future acquisitions may also require us to obtain additional financing, which may not be available on favorable terms or at all. These transactions may never be successful and may require significant time and attention of management. In addition, the integration of any business that we may acquire in the future may disrupt our existing business and may be a complex, risky and costly endeavor for which we may never realize the full benefits of the acquisition.

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

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

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

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

Our corporate headquarters and other facilities are located in the San Francisco Bay Area, which in the past has experienced both severe earthquakes and wildfires. We do not carry earthquake insurance. Earthquakes, wildfires or other natural disasters could severely disrupt our operations, and have a material adverse effect on our business, results of operations, financial condition and prospects.

If a natural disaster, power outage, outbreak of disease, or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as our enterprise financial systems or manufacturing resource planning and enterprise quality systems, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible, for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place currently are limited and are unlikely to prove adequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which, particularly when taken together with our lack of earthquake insurance, could have a material adverse effect on our business.

Furthermore, integral parties used in our preclinical activities and in our supply chain are similarly vulnerable to natural disasters, outbreak of disease, or other sudden, unforeseen and severe adverse events. If such an event were to affect our preclinical activities or our supply chain, it could have a material adverse effect on our business.

Epidemic and pandemic diseases, such as COVID-19, or the perception of their effects, could have a material adverse effect on our business, financial condition, results of operations or cash flows.

Outbreaks of epidemic, pandemic or contagious diseases, such as the recent SAR-CoV-2 virus, or, historically, the Ebola virus, Middle East Respiratory Syndrome, Severe Acute Respiratory Syndrome or the H1N1 virus, could significantly disrupt our business. Such outbreaks pose the risk that we or our employees, contractors, suppliers, and other partners may be prevented from conducting business activities for an indefinite period of time due to spread of the disease within these groups, or due to shutdowns that may be requested or mandated by federal, state and local governmental authorities. Business disruptions could include disruptions or

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restrictions on our ability to travel, as well as temporary closures of our facilities and the facilities of our partners, clinical trial sites, service providers, suppliers or contract manufacturers. While it is not possible at this time to estimate the overall impact that COVID-19 will have on our business, the continued rapid spread of COVID-19, both across the United States and through much of the world, and the measures taken by the governments of countries and local authorities affected could disrupt and delay our ongoing clinical trials, our preclinical activities, the manufacture or shipment of both drug substance and finished drug product for our product candidates for preclinical testing and clinical trials and adversely impact our business, financial condition or results of operations.

For example, as a result of the COVID-19 pandemic, the state of California, where our corporate offices are located, has issued orders for all residents to remain at home, except as needed for essential activities, and we have had to implement work from home policies that may continue for an indefinite period. We have taken steps to ensure the safety of our patients and employees, while working to ensure the sustainability of our business operations as this unprecedented situation continues to evolve. We continue to evaluate the impact of COVID-19 on the healthcare system and work with healthcare providers supporting our clinical studies to mitigate risk to patients while taking into account regulatory, institutional, and government guidance and policies. All of our clinical trial sites for our RMC-4630 clinical studies are currently located in the U.S., and may be affected by the COVID-19 outbreak due to prioritization of hospital resources toward the COVID-19 outbreak, travel or quarantine restrictions imposed by federal, state or local governments, and the inability to access sites for initiation and patient monitoring and enrollment. As a result, patient screening, new patient enrollment, monitoring and data collection may be affected or delayed. We are aware of several clinical sites involved in our RMC-4630 clinical studies that have temporarily stopped or delayed enrolling new patients, with exemptions if appropriate. These developments may delay our clinical trial timelines. Some of our third-party manufacturers which we use for the supply of materials for product candidates or other materials necessary to manufacture product to conduct preclinical tests and clinical trials are located in countries affected by COVID-19, and should they experience continued disruptions, such as temporary closures or suspension of services, we would likely experience delays in advancing clinical trials. Currently, we expect no material impact on the clinical supply of RMC-4630. Furthermore, the spread of the virus may affect the operations of key governmental agencies, such as the FDA, which may delay the development of our product candidates. The spread of an infectious disease, including COVID-19, may also result in the inability of our suppliers to deliver components or raw materials on a timely basis or at all. Such events may result in a period of business disruption, and in reduced operations, or doctors and medical providers may be unwilling to participate in our clinical trials, any of which could materially affect our business, financial condition and results of operations.

In addition, a significant outbreak of epidemic, pandemic or contagious diseases in the human population, such as the global COVID-19 pandemic, could result in a widespread health crisis and adversely affect the economies and financial markets of many countries, resulting in an economic downturn that could affect demand for our current or future products. Any of these events could have a material adverse effect on our business, financial condition, results of operations or cash flows.

Our internal computer systems, or those used by our CROs or other contractors or consultants, may fail or suffer security breaches.

Despite the implementation of security measures, our internal computer systems and those of our future CROs and other contractors and consultants are vulnerable to damage from computer viruses and unauthorized access. While we have not to our knowledge experienced any such material system failure or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our marketing approval efforts and significantly increase our costs to recover or reproduce the data. Likewise, we rely on third parties for the manufacture of

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our product candidates and to conduct clinical trials, and similar events relating to their computer systems could also have a material adverse effect on our business. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development and commercialization of our future product candidates could be delayed.

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

We are exposed to the risk that our employees, independent contractors, vendors, principal investigators, CROs and consultants may engage in fraudulent conduct or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct or disclosure of unauthorized activities to us that violate the regulations of the FDA and comparable foreign regulatory authorities, including those laws requiring the reporting of true, complete and accurate information to such authorities; healthcare fraud and abuse laws and regulations in the United States and abroad; or laws that require the reporting of financial information or data accurately. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Activities subject to these laws also involve the improper use of information obtained in the course of clinical trials or creating fraudulent data in our preclinical studies or clinical trials, which could result in regulatory sanctions and cause serious harm to our reputation. It is not always possible to identify and deter misconduct by employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. Additionally, we are subject to the risk that a person could allege such fraud or other misconduct, even if none occurred. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

Risks related to our common stock and this offering

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

The public offering price of our common stock is substantially higher than the as adjusted net tangible book value per share of our common stock. Therefore, if you purchase our common stock in this offering, you will pay a price per share that substantially exceeds the as adjusted net tangible book value per share after the completion of this offering. Based on an assumed public offering price of \$ _____ per share, which is the last reported sale price of our common stock on the Nasdaq Global Select Market on _____, 2020, you will experience immediate dilution of \$ _____ per share, representing the difference between our as adjusted net tangible book value per share as of March 31, 2020 and the assumed public offering price. Furthermore, if the underwriters exercise their option to purchase additional shares, or outstanding options are exercised, you could experience further dilution. See "Dilution" for a more detailed description of the dilution to new investors in the offering.

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The price of our common stock is volatile and fluctuate substantially, which could result in substantial losses for purchasers of our common stock in this offering.

Our stock price is highly volatile. The stock market in general and the market for biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, you may not be able to sell your common stock at or above the public offering price. The market price for our common stock may be influenced by many factors, including:

- the success of competitive products or technologies;
- results of clinical trials and preclinical studies or those of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to our product candidates or clinical development programs;
- the results of our efforts to discover, develop, acquire or in-license product candidates or companion diagnostics;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors; and
- general economic, industry and market conditions.

In addition, the trading prices for common stock of other biopharmaceutical companies have been highly volatile as a result of the COVID-19 pandemic. The COVID-19 pandemic continues to rapidly evolve. The extent to which the pandemic may impact our business, preclinical studies and clinical trials will depend on future developments, which are highly uncertain and cannot be predicted with confidence.

An active trading market for our common stock may not be sustained, and you may not be able to resell your shares at or above the public offering price.

Prior to our IPO in February 2020, there was no public market for shares of our common stock. Shares of our common stock only recently began trading on the Nasdaq Global Select Market, but we can provide no assurance that we will be able to sustain an active trading market for our shares. The public offering price of our common stock has been determined through negotiations between us and the underwriters. This public offering price may not be indicative of the market price of our common stock after this offering. In the absence of an active trading market for our common stock, investors may not be able to sell their common stock at or above the public offering price or at the time that they would like to sell.

We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock.

We do not currently intend to pay any cash dividends on our common stock for the foreseeable future. We currently intend to invest our future earnings, if any, to fund our growth. Therefore, you are not likely to receive any dividends on your common stock for the foreseeable future. Since we do not intend to pay dividends, your

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ability to receive a return on your investment will depend on any future appreciation in the market value of our common stock. There is no guarantee that our common stock will appreciate or even maintain the price at which our holders have purchased it.

We are an emerging growth company, and we cannot be certain if the reduced reporting requirements applicable to emerging growth companies will make our common stock less attractive to investors.

We are an emerging growth company, as defined in the JOBS Act. For as long as we continue to be an emerging growth company, we may take advantage of exemptions from various reporting requirements, that are applicable to other public companies that are not emerging growth companies, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation and exemptions from the requirements of holding nonbinding advisory votes on executive compensation and stockholder approval of any golden parachute payments not previously approved. We could be an emerging growth company for up to five years following the year in which we completed our initial public offering, although circumstances could cause us to lose that status earlier. We will remain an emerging growth company until the earlier of (1) December 31, 2025, (2) the last day of the fiscal year in which we have total annual gross revenue of at least \$1.07 billion, (3) the last day of the fiscal year in which we are deemed to be a large accelerated filer, which requires the market value of our common stock that is held by non-affiliates to exceed \$700.0 million as of the prior June 30th, or (4) the date on which we have issued more than \$1.0 billion in non-convertible debt during the prior three-year period. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

Under the JOBS Act, emerging growth companies can also delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have elected to use the extended transition period for any other new or revised accounting standards during the period in which we remain an emerging growth company; however, we may adopt certain new or revised accounting standards early. As a result, changes in rules of U.S. generally accepted accounting principles or their interpretation, the adoption of new guidance or the application of existing guidance to changes in our business could significantly affect our financial position and results of operations.

Our executive officers, directors and their affiliates have significant influence over our company, which will limit your ability to influence corporate matters and could delay or prevent a change in corporate control.

As of March 31, 2020, our executive officers, directors and their affiliates beneficially own, in the aggregate, approximately 43% of our outstanding common stock. As a result, these stockholders, if they act together, will be able to influence our management and affairs and the outcome of matters submitted to our stockholders for approval, including the election of directors and any sale, merger, consolidation or sale of all or substantially all of our assets. In addition, this concentration of ownership might adversely affect the market price of our common stock by:

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

See “Security Ownership of Certain Beneficial Owners and Management” as stated in our Annual Report on Form 10-K for the year ended December 31, 2019, incorporated by reference in this prospectus, for more information regarding the ownership of our outstanding common stock by our executive officers, directors and their affiliates.

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We have broad discretion in how we use the proceeds of this offering and may not use these proceeds effectively, which could affect our results of operations and cause our stock price to decline.

We will have considerable discretion in the application of the net proceeds from this offering. As a result, investors will be relying upon management's judgment with only limited information about our specific intentions for the use of the net proceeds from this offering. We may use the net proceeds from this offering for purposes that do not yield a significant return or any return at all for our stockholders. In addition, pending their use, we may invest the net proceeds from this offering in a manner that does not produce income or that loses value.

We incur significantly increased costs as a result of operating as a public company, and our management is required to devote substantial time to new compliance initiatives.

As a public company, we incur significant legal, accounting and other expenses that we did not incur as a private company. We are subject to the reporting requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act, which requires, among other things, that we file with the U.S. Securities and Exchange Commission, or the SEC, annual, quarterly and current reports with respect to our business and financial condition. In addition, the Sarbanes-Oxley Act, as well as rules subsequently adopted by the SEC and Nasdaq to implement provisions of the Sarbanes-Oxley Act, impose significant requirements on public companies, including requiring establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. Further, in July 2010, the Dodd-Frank Wall Street Reform and Consumer Protection Act, or the Dodd-Frank Act, was enacted. There are significant corporate governance and executive compensation-related provisions in the Dodd-Frank Act that require the SEC to adopt additional rules and regulations in these areas such as "say on pay" and proxy access. Recent legislation permits emerging growth companies to implement many of these requirements over a longer period and up to five years from the pricing of their IPO. We intend to take advantage of this legislation, but cannot guarantee that we will not be required to implement these requirements sooner than budgeted or planned and thereby incur unexpected expenses. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business in ways we cannot currently anticipate.

We expect the rules and regulations applicable to public companies to substantially increase our legal and financial compliance costs and to make some activities more time-consuming and costly. If these requirements divert the attention of our management and personnel from other business concerns, they could have a material adverse effect on our business, financial condition, results of operations and prospects. The increased costs will decrease our net income or increase our net loss, and may require us to reduce costs in other areas of our business or increase the prices of our products or services. For example, we expect these rules and regulations to make it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to incur substantial costs to maintain the same or similar coverage. We cannot predict or estimate the amount or timing of additional costs we may incur to respond to these requirements. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers.

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

If our existing stockholders sell, or indicate an intention to sell, substantial amounts of our common stock in the public market, the market price of our common stock could decline. As of March 31, 2020, we had outstanding 59,003,644 shares of common stock. The resale of 42,895,971 shares, or 73% of our outstanding shares of

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common stock is currently prohibited or otherwise restricted as a result of securities law provisions, market standoff agreements entered into by certain of our stockholders with us or lock-up agreements entered into by our stockholders with the underwriters in connection with our IPO.

The lock-up agreements with the underwriters pertaining to our IPO or market stand-off provisions in agreements with us will expire after August 11, 2020. J.P. Morgan Securities LLC may, in its sole discretion, permit our stockholders who are subject to these lock-up agreements to sell shares prior to the expiration of the lock-up agreements. After the lock-up agreements with the underwriters of our IPO or market stand-off provisions in agreements with us expire, the shares of common stock will be eligible for sale in the public market. Approximately 55% of these additional shares are held by directors, executive officers and other affiliates and will be subject to certain limitations of Rule 144 under the Securities Act of 1933, as amended, or the Securities Act.

In addition, we and our executive officers and directors have entered into lock-up agreements with the underwriters under which 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 _____ for a period of _____ days following the date of this prospectus. When this lock-up period expires, we and our securityholders subject to a lock-up agreement could sell shares in the public market, which could cause our stock price to fall. _____ may, in its sole discretion, permit our stockholders who are subject to these lock-up agreements to sell shares prior to the expiration of the lock-up agreements. See the description of the lock-up agreement with the underwriters of this offering in the section titled "Shares eligible for future sale" for more information. Sales of a substantial number of such shares upon expiration of the lock-up agreements, 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.

As of March 31, 2020, 11,207,358 shares of common stock that are either subject to outstanding options or reserved for future issuance under our equity incentive plans will become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules, the lock-up agreements, market stand-off provisions in agreements with us and Rule 144 and Rule 701 under the Securities Act. If these additional shares of common stock are sold, or if it is perceived that they will be sold, in the public market, the market price of our common stock could decline.

In addition, the holders of approximately 39.6 million shares of our common stock are entitled to rights with respect to the registration of their shares under the Securities Act, subject to the lock-up agreements described above. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act, except for shares purchased by affiliates. Any sales of securities by these stockholders could have a material adverse effect on the market price of our common stock.

Our ability to utilize our net operating loss carryforwards and certain other tax attributes has been limited by "ownership changes" and may be further limited.

Under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or the Code, and corresponding provisions of state law, if a corporation undergoes an "ownership change" (generally defined as a greater than 50 percentage point change (by value) in its equity ownership over a rolling three-year period), the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change income may be limited. We have experienced ownership changes in the past, and we may experience ownership changes in the future as a result of this offering or other changes in our stock ownership (some of which are not in our control). Use of our federal and state net operating loss carryforwards have been limited and could be further limited if we experience additional ownership changes, which could have an adverse effect on our future results of operations.

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If we sell shares of our common stock in future financings, stockholders may experience immediate dilution and, as a result, our stock price may decline.

We may from time to time issue additional shares of common stock at a discount from the current trading price of our common stock. As a result, our stockholders would experience immediate dilution upon the purchase of any shares of our common stock sold at such discount. In addition, as opportunities present themselves, we may enter into financing or similar arrangements in the future, including the issuance of debt securities, preferred stock or common stock. If we issue common stock or securities convertible into common stock, our common stockholders would experience additional dilution and, as a result, our stock price may decline.

If securities analysts do not continue to publish research or reports about our business or if they publish negative evaluations of our stock, the price of our stock could decline.

The trading market for our common stock relies, in part, on the research and reports that industry or financial analysts publish about us or our business. If few analysts publish research or reports about us, the trading price of our stock would likely decrease. If one or more of the analysts covering our business downgrade their evaluations of our stock, the price of our stock could decline. If one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which, in turn, could cause our stock price to decline.

If we fail to maintain proper and effective internal control over financial reporting, our ability to produce accurate and timely financial statements could be impaired, investors may lose confidence in our financial reporting and the trading price of our common stock may decline.

Pursuant to Section 404 of Sarbanes-Oxley, our management is required to report upon the effectiveness of our internal control over financial reporting beginning with the annual report for our fiscal year ending December 31, 2021. When we lose our status as an “emerging growth company,” our independent registered public accounting firm will be required to attest to the effectiveness of our internal control over financial reporting. The rules governing the standards that must be met for management to assess our internal control over financial reporting are complex and require significant documentation, testing and possible remediation. To comply with the requirements of being a reporting company under the Exchange Act, we will need to implement additional financial and management controls, reporting systems and procedures and hire additional accounting and finance staff.

We cannot assure you that there will not be material weaknesses in our internal control over financial reporting in the future. Any failure to implement and maintain internal control over financial reporting could severely inhibit our ability to accurately report our financial condition, results of operations or cash flows. If we are unable to conclude that our internal control over financial reporting is effective, or if our independent registered public accounting firm determines we have a material weakness in our internal control over financial reporting, investors may lose confidence in the accuracy and completeness of our financial reports, the market price of our common stock could decline, and we could be subject to sanctions or investigations by Nasdaq, the SEC or other regulatory authorities. Failure to remedy any material weakness in our internal control over financial reporting, or to implement or maintain other effective control systems required of public companies, could also restrict our future access to the capital markets.

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Provisions in our charter documents and under Delaware law could discourage a takeover that stockholders may consider favorable and may lead to entrenchment of management.

Our amended and restated certificate of incorporation and amended and restated bylaws contain provisions that could delay or prevent changes in control or changes in our management without the consent of our board of directors. These provisions include the following:

- a classified board of directors with three-year staggered terms, which may delay the ability of stockholders to change the membership of a majority of our board of directors;
- no cumulative voting in the election of directors, which limits the ability of minority stockholders to elect director candidates;
- the exclusive right of our board of directors to elect a director to fill a vacancy created by the expansion of the board of directors or the resignation, death or removal of a director, which prevents stockholders from being able to fill vacancies on our board of directors;
- the ability of our board of directors to authorize the issuance of shares of preferred stock and to determine the price and other terms of those shares, including preferences and voting rights, without stockholder approval, which could be used to significantly dilute the ownership of a hostile acquiror;
- the ability of our board of directors to alter our amended and restated bylaws without obtaining stockholder approval;
- the required approval of at least 66 2/3% of the shares entitled to vote at an election of directors to adopt, amend or repeal our amended and restated bylaws or repeal the provisions of our amended and restated certificate of incorporation regarding the election and removal of directors;
- a prohibition on stockholder action by written consent, which forces stockholder action to be taken at an annual or special meeting of our stockholders;
- the requirement that a special meeting of stockholders may be called only by our chief executive officer or president or by the board of directors, which may delay the ability of our stockholders to force consideration of a proposal or to take action, including the removal of directors; and
- advance notice procedures that stockholders must comply with in order to nominate candidates to our board of directors or to propose matters to be acted upon at a stockholders' meeting, which may discourage or deter a potential acquiror from conducting a solicitation of proxies to elect the acquiror's own slate of directors or otherwise attempting to obtain control of us.

We are also subject to the anti-takeover provisions contained in Section 203 of the Delaware General Corporation Law. Under Section 203, a corporation may not, in general, engage in a business combination with any holder of 15% or more of its capital stock unless the holder has held the stock for three years or, among other exceptions, the board of directors has approved the transaction. For a description of our capital stock, see the section titled "Description of capital stock."

Claims for indemnification by our directors and officers may reduce our available funds to satisfy successful third-party claims against us and may reduce the amount of money available to us.

Our amended and restated certificate of incorporation and amended and restated bylaws provide that we will indemnify our directors and officers, in each case to the fullest extent permitted by Delaware law.

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In addition, as permitted by Section 145 of the Delaware General Corporation Law, our amended and restated bylaws and our indemnification agreements that we have entered into with our directors and officers provide that:

- we will indemnify our directors and officers for serving us in those capacities or for serving other business enterprises at our request, to the fullest extent permitted by Delaware law. Delaware law provides that a corporation may indemnify such person if such person acted in good faith and in a manner such person reasonably believed to be in or not opposed to the best interests of the registrant and, with respect to any criminal proceeding, had no reasonable cause to believe such person's conduct was unlawful;
- we may, in our discretion, indemnify employees and agents in those circumstances where indemnification is permitted by applicable law;
- we are required to advance expenses, as incurred, to our directors and officers in connection with defending a proceeding, except that such directors or officers shall undertake to repay such advances if it is ultimately determined that such person is not entitled to indemnification;
- we are not obligated pursuant to our amended and restated bylaws to indemnify a person with respect to proceedings initiated by that person against us or our other indemnitees, except with respect to proceedings authorized by our board of directors or brought to enforce a right to indemnification;
- the rights conferred in our amended and restated bylaws are not exclusive, and we are authorized to enter into indemnification agreements with our directors, officers, employees and agents and to obtain insurance to indemnify such persons; and
- we may not retroactively amend our amended and restated bylaw provisions to reduce our indemnification obligations to directors, officers, employees and agents.

Our amended and restated certificate of incorporation and amended and restated bylaws provide for an exclusive forum in the Court of Chancery of the State of Delaware for certain disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our amended and restated certificate of incorporation and amended and restated bylaws provide that the Court of Chancery of the State of Delaware is the exclusive forum for any state law derivative action or proceeding brought on our behalf, any action asserting a breach of fiduciary duty, any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, any action to interpret, apply, enforce, or determine the validity of our amended and restated certificate of incorporation or our amended and restated bylaws, or any action asserting a claim against us that is governed by the internal affairs doctrine; provided that, the exclusive forum provision will not apply to suits brought to enforce any liability or duty created by the Securities Act or the Exchange Act or any other claim for which the federal courts have exclusive jurisdiction; and provided further that, if and only if the Court of Chancery of the State of Delaware dismisses any such action for lack of subject matter jurisdiction, such action may be brought in another state or federal court sitting in the State of Delaware. Nothing in our amended and restated certificate of incorporation or amended and restated bylaws preclude stockholders that assert claims under the Securities Act or the Exchange Act from bringing such claims in state or federal court, subject to applicable law.

We believe these provisions may benefit us by providing increased consistency in the application of Delaware law and federal securities laws by chancellors and judges, as applicable, particularly experienced in resolving corporate disputes, efficient administration of cases on a more expedited schedule relative to other forums and protection against the burdens of multi-forum litigation. This choice of forum provision may limit a

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stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or any of our directors, officers, other employees or stockholders, which may discourage lawsuits with respect to such claims, although our stockholders will not be deemed to have waived our compliance with federal securities laws and the rules and regulations thereunder. If a court were to find the choice of forum provision in our amended and restated certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our business, financial condition, results of operations and prospects.

Special note regarding forward-looking statements

This prospectus contains forward-looking statements concerning our business, operations and financial performance and condition, as well as our plans, objectives and expectations for our business, operations and financial performance and condition. Any statements contained herein that are not statements of historical facts may be deemed to be forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as “aim,” “anticipate,” “assume,” “believe,” “contemplate,” “continue,” “could,” “due,” “estimate,” “expect,” “goal,” “intend,” “may,” “objective,” “plan,” “predict,” “potential,” “positioned,” “seek,” “should,” “target,” “will,” “would,” and other similar expressions that are predictions of or indicate future events and future trends, or the negative of these terms or other comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- the scope, progress, results and costs of developing our product candidates or any other future product candidates, and conducting preclinical studies and clinical trials, including our RMC-4630 Phase 1/2 clinical program;
- the scope, progress, results and costs related to the research and development of our pipeline;
- the timing of and costs involved in obtaining and maintaining regulatory approval for any of current or future product candidates, and any related restrictions, limitations and/or warnings in the label of an approved product candidate;
- our expectations regarding the potential market size and size of the potential patient populations for RMC-4630, our other product candidates and any future product candidates, if approved for commercial use;
- our ability to maintain existing and establish new collaborations, licensing or other arrangements and the financial terms of any such agreements, including our collaboration with Sanofi;
- our commercialization, marketing and manufacturing capabilities and expectations;
- the rate and degree of market acceptance of our product candidates, as well as the pricing and reimbursement of our product candidates, if approved;
- the implementation of our business model and strategic plans for our business, product candidates and technology, including additional indications for which we may pursue;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates, including the projected term of patent protection;
- estimates of our expenses, future revenue, capital requirements, our needs for additional financing and our ability to obtain additional capital;
- developments and projections relating to our competitors and our industry, including competing therapies and procedures;
- regulatory and legal developments in the United States and foreign countries;
- the performance of our third-party suppliers and manufacturers;
- the impact of COVID-19 on our business and operations, including clinical trials, manufacturing, use of contract research organizations and employees;
- our ability to attract and retain key scientific or management personnel;

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- our expectations regarding the period during which we will qualify as an emerging growth company under the Jumpstart Our Business Startups Act of 2012;
- our expectations regarding our ability to obtain, maintain, enforce and defend our intellectual property protection for our product candidates;
- our use of proceeds from this offering; and
- other risks and uncertainties, including those listed under the caption “Risk factors” and elsewhere and incorporated by reference in this prospectus

These forward-looking statements are based on management’s current expectations, estimates, forecasts and projections about our business and the industry in which we operate and management’s beliefs and assumptions and are not guarantees of future performance or development and involve known and unknown risks, uncertainties and other factors that are in some cases beyond our control. As a result, any or all of our forward-looking statements in, or incorporated by reference in, this prospectus may turn out to be inaccurate. Factors that may cause actual results to differ materially from current expectations include, among other things, those listed under “Risk factors” and elsewhere and incorporated by reference in this prospectus. Potential investors are urged to consider these factors carefully in evaluating the forward-looking statements. These forward-looking statements speak only as of the date of this prospectus. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future. You should, however, review the factors and risks we describe in the reports we will file from time to time with the SEC after the date of this prospectus. See “Where you can find more information.”

Market and industry data

This prospectus, including the information incorporated by reference herein, contains estimates, projections and other information concerning our industry and, business, as well as data regarding market research, estimates and forecasts prepared by our management. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances that are assumed in this information. Unless otherwise expressly stated, we obtained this industry, business, market and other data from reports, research surveys, studies and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data and similar sources. In some cases, we do not expressly refer to the sources from which this data is derived. In that regard, when we refer to one or more sources of this type of data in any paragraph, you should assume that other data of this type appearing in the same paragraph is derived from the same sources, unless otherwise expressly stated or the context otherwise requires.

This industry, business, market and other information involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. We have not independently verified any third-party information and cannot assure you of its accuracy or completeness. Although we are responsible for all of the disclosure contained in this prospectus and we believe the market position, market opportunity, market size and other information included in this prospectus is reliable, such information is inherently imprecise. In addition, projections, assumptions and estimates of our future performance and the future performance of the industry in which we operate is necessarily subject to a high degree of uncertainty and risk due to a variety of factors, including those described in the section titled "Risk factors" and elsewhere in this prospectus. These and other factors could cause results to differ materially from those expressed in the estimates made by the independent parties and by us.

Use of proceeds

We estimate that the net proceeds from the sale of _____ shares of our common stock in this offering will be approximately \$ _____ million at the assumed public offering price of \$ _____ per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on _____, 2020, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us. If the underwriters exercise their option to purchase additional shares in full, we estimate that the net proceeds will be approximately \$ _____ million at the assumed public offering price of \$ _____ per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on _____, 2020, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

Each \$1.00 increase (decrease) in the assumed public offering price of \$ _____ per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on _____, 2020, would increase (decrease) the net proceeds to us from this offering, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, by approximately \$ _____ million, assuming that the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same. We may also increase or decrease the number of shares we are offering. Each increase (decrease) of 1,000,000 in the number of shares we are offering would increase (decrease) the net proceeds to us from this offering, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, by approximately \$ _____ million, assuming the assumed public offering price stays the same. We do not expect that a change in the offering price or the number of shares by these amounts would have a material effect on our intended uses of the net proceeds from this offering, although it may impact the amount of time prior to which we may need to seek additional capital.

We currently expect to use our net proceeds from this offering, together with our existing cash, cash equivalents and marketable securities, to fund the development of our multiple RAS programs, including our RAS(ON) portfolio and our SOS1 program, and our 4EBP1/mTORC1 program and other general corporate purposes, which may include the hiring of additional personnel, capital expenditures and the costs of operating as a public company.

Under our collaboration with Sanofi, Sanofi is responsible for reimbursing substantially all of our research costs and all of our development costs for the SHP2 program. We may also use a portion of the remaining net proceeds from this offering and our existing cash, cash equivalents and marketable securities to in-license, acquire or invest in complementary businesses, technologies, products or assets. However, we have no current commitments or obligations to do so.

Due to the uncertainties inherent in the clinical development and regulatory approval process, it is difficult to estimate with certainty the exact amounts of the net proceeds from this offering that may be used for the above purposes. As such, our management will retain broad discretion over the use of the net proceeds from this offering. The amounts and timing of our expenditures may depend upon numerous factors, including: (i) continued research and development SHP2 program reimbursement by Sanofi under the Sanofi Agreement; (ii) the time and cost necessary to advance our product candidates through clinical trials and future clinical trials; (iii) the time and cost associated with our research and development activities for our pipeline; (iv) the time and cost associated with the manufacture and supply of product candidates for clinical development or commercialization; and (v) our ability to obtain regulatory approval for and subsequently commercialize our product candidates.

We believe that the net proceeds from this offering, together with our existing cash, cash equivalents and marketable securities, will enable us to fund our operations for at least 12 months following the date of this

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offering. After this offering, we will require substantial capital in order to advance our current and future product candidates through clinical trials, regulatory approval and, if approved, commercialization. For additional information regarding our potential capital requirements, see “Risk factors—Even if this offering is successful, we will require substantial additional financing to achieve our goals, which may not be available on acceptable terms, or at all. A failure to obtain this necessary capital when needed could force us to delay, limit, reduce or terminate our product development or commercialization efforts.”

Pending the use of the proceeds from this offering, we intend to invest the net proceeds in interest-bearing, investment-grade securities, certificates of deposit or government securities.

Dividend policy

We have never declared or paid cash dividends on our capital stock. We intend to retain all available funds and any future earnings, if any, to fund the development and expansion of our business, and we do not anticipate paying any cash dividends in the foreseeable future. Any future determination related to dividend policy will be made at the discretion of our board of directors and will depend upon, among other factors, our results of operations, financial condition, capital requirements, contractual restrictions, business prospects and other factors our board of directors might deem relevant.

Capitalization

The following table sets forth our cash, cash equivalents and marketable securities and capitalization as of March 31, 2020:

- on an actual basis;
- on an as adjusted basis to give effect to the sale of _____ shares of common stock in this offering at the assumed public offering price of \$ _____ per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on _____, 2020, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

You should read this table together with the section of this prospectus entitled “Management’s discussion and analysis of financial condition and results of operations” and our consolidated financial statements and related notes incorporated by reference in this prospectus.

	As of March 31, 2020	
	Actual	As Adjusted(1)
	(in thousands, except share and per share data)	
Cash, cash equivalents and marketable securities	\$ 347,948	\$
Stockholders’ equity:		
Common stock, \$0.0001 par value per share; 300,000,000 shares authorized, 59,003,644 shares issued and outstanding, actual; 300,000,000 shares authorized, _____ shares issued and outstanding, as adjusted		6
Additional paid-in capital	562,179	
Accumulated other comprehensive income	36	
Accumulated deficit	(176,905)	
Total stockholders’ equity	385,316	
Total capitalization	\$ 385,316	\$

(1) A \$1.00 increase (decrease) in the assumed public offering price of \$ _____ per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on _____, 2020, would increase (decrease) the amount of each of cash, cash equivalents and marketable securities, additional paid-in capital, total stockholders’ equity and total capitalization by approximately \$ _____ million, assuming the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same and after deducting underwriting discounts and commissions and estimated offering expenses payable by us. We may also increase or decrease the number of shares we are offering. Each increase (decrease) of 1,000,000 shares in the number of shares offered by us would increase (decrease) each of cash, cash equivalents and marketable securities, additional paid-in capital, total stockholders’ equity and total capitalization by approximately \$ _____ million, assuming the assumed public offering price of \$ _____ per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on _____, 2020, remains the same, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us. The as adjusted information discussed above is illustrative only and will be adjusted based on the actual public offering price and other terms of this offering determined at pricing.

The outstanding share information in the table above excludes the following:

- 5,568,324 shares of common stock issuable upon the exercise of outstanding stock options as of March 31, 2020 having a weighted-average exercise price of \$5.29 per share;
- _____ shares of common stock issuable upon the exercise of stock options granted after March 31, 2020 having a weighted-average exercise price of \$_____ per share;
- 5,110,075 shares of common stock reserved for issuance pursuant to future awards under our 2020 Incentive Award Plan, as well as any automatic increases in the number of shares of common stock reserved for future issuance under this plan; and
- 528,959 shares of common stock reserved for issuance under our 2020 Employee Stock Purchase Plan, as well as any automatic increases in the number of shares of our common stock reserved for future issuance under this plan.

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Dilution

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

As of March 31, 2020, we had a historical net tangible book value of \$309.0 million, or \$5.24 per share of common stock. Our net tangible book value represents total tangible assets less total liabilities, all divided by 59,003,644 shares of common stock outstanding on March 31, 2020.

After giving effect to the sale of _____ shares of common stock in this offering at an assumed public offering price of \$ _____ per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on _____, 2020, and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of March 31, 2020 would have been \$ _____ million, or \$ _____ per share. This represents an immediate increase in as adjusted net tangible book value of \$ _____ per share to existing stockholders and an immediate dilution of \$ _____ per share to new investors. The following table illustrates this per share dilution:

Assumed public offering price per share	\$
Historical net tangible book value per share as of March 31, 2020	\$5.24
Increase in net tangible book value per share attributable to new investors purchasing shares in this offering	_____
As adjusted net tangible book value per share after this offering	_____
Dilution per share to new investors purchasing shares in this offering	\$

Each \$1.00 increase (decrease) in the assumed public offering price of \$ _____ per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on _____, 2020, would increase (decrease) our as adjusted net tangible book value as of March 31, 2020 after this offering by approximately \$ _____ million, or approximately \$ _____ per share, and would increase (decrease) dilution to investors in this offering by approximately \$ _____ per share, assuming that the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us. We may also increase or decrease the number of shares we are offering. Assuming the assumed public price of \$ _____ per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on _____, 2020, remains the same, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, each increase of 1,000,000 in the number of shares we are offering would increase our as adjusted net tangible book value as of March 31, 2020 after this offering by approximately \$ _____ million, or approximately \$ _____ per share, and would decrease dilution to investors in this offering by approximately \$ _____ per share, and a decrease of 1,000,000 in the number of shares we are offering would decrease our as adjusted net tangible book value as of March 31, 2020 after this offering by approximately \$ _____ million, or approximately \$ _____ per share, and would increase dilution to investors in this offering by approximately \$ _____ per share. The as adjusted information is illustrative only, and we will adjust this information based on the actual public offering price and other terms of this offering determined at pricing.

If the underwriters fully exercise their option to purchase additional shares, as adjusted net tangible book value after this offering would increase to approximately \$ _____ per share, and there would be an immediate dilution of approximately \$ _____ per share to new investors.

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To the extent that outstanding options with an exercise price per share that is less than the as adjusted net tangible book value per share are exercised, new investors will 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 we raise additional capital through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to our stockholders.

The foregoing tables and calculations above are based on 59,003,644 shares of common stock outstanding as of March 31, 2020 and exclude the following:

- 5,568,324 shares of common stock issuable upon the exercise of outstanding stock options as of March 31, 2020 having a weighted-average exercise price of \$5.29 per share;
- _____ shares of common stock issuable upon the exercise of stock options granted after March 31, 2020 having a weighted-average exercise price of \$ _____ per share;
- 5,110,075 shares of common stock reserved for issuance pursuant to future awards under our 2020 Incentive Award Plan, as well as any automatic increases in the number of shares of common stock reserved for future issuance under this plan; and
- 528,959 shares of common stock reserved for issuance under our 2020 Employee Stock Purchase Plan, as well as any automatic increases in the number of shares of our common stock reserved for future issuance under this plan.

Business

Overview

We are a clinical-stage precision oncology company focused on developing novel targeted therapies to inhibit elusive, high-value *frontier* targets within notorious growth and survival pathways, with particular emphasis on the RAS and mTOR signaling pathways. We define *frontier* targets as proteins that play an important role in cancer and for which there is either: (1) no approved drug that directly **inhibits** it, or (2) one or more approved drugs that directly inhibit it but through a mechanism of action that may not enable **suppression of the full range of its biologic contributions to cancer**.

Our understanding of genetic drivers and adaptive resistance mechanisms in cancer, coupled with robust drug discovery and medicinal chemistry capabilities, has guided us to establish a deep pipeline targeting critical signaling nodes within these pathways. This cohesive approach underpins our clinical strategy of exploring mechanism-based dosing paradigms and in-pathway combinations to optimize treatment for cancer patients. Our most advanced product candidate, RMC-4630, is a potent and selective inhibitor of SHP2, based on preclinical evidence described in this prospectus. SHP2 is a central node in the RAS signaling pathway. In collaboration with Sanofi, we are evaluating RMC-4630 in a multi-cohort Phase 1/2 clinical program.

This RMC-4630 Phase 1/2 program currently consists of three active clinical trials: RMC-4630-01, a Phase 1 study of RMC-4630 as a single agent, and RMC-4630-02, a Phase 1b/2 study of RMC-4630 in combination with the MEK inhibitor cobimetinib (Cotellic), and an Amgen sponsored Phase 1b study of RMC-4630 in combination with Amgen's KRAS^{G12C}(OFF) inhibitor, AMG 510 or sotorasib. In this prospectus, we include preliminary data from 87 patients who had enrolled in our Phase 1 study and received RMC-4630 as a monotherapy as of May 4, 2020.

Clinical data from the first eight patients enrolled in our Phase 1b/2 combination study and treated before November 2019 is provided. Enrollment has continued in additional dose cohorts in this ongoing study.

Our most advanced product candidate, RMC-4630, is a potent and selective inhibitor of SHP2, based on preclinical evidence described in this prospectus. SHP2 is a protein that plays a central role in modulating cell survival and growth by transmitting signals from upstream receptor tyrosine kinases, or RTKs, to RAS. In collaboration with Sanofi, we are evaluating RMC-4630 in a multi-cohort Phase 1/2 clinical program, which includes our ongoing Phase 1 study of RMC-4630 as monotherapy in patients with advanced cancers, including those with tumors harboring genetically defined mutations in the RAS signaling pathway and our ongoing Phase 1b/2 study of RMC-4630 in combination with the MEK inhibitor cobimetinib. Amgen is evaluating RMC-4630 in combination with the investigational KRAS^{G12C}(OFF) inhibitor sotorasib in patients with advanced cancers with tumors harboring KRAS^{G12C} mutations. Based on our own data, and supported by observations by others, we are evaluating intermittent dosing schedules in our clinical program to allow us to maximize dose intensity in order to achieve the greatest depth of response.

We also plan to explore the potential clinical benefit of RMC-4630 in combination with other in-pathway agents such as osimertinib (a third-generation inhibitor of epidermal growth factor receptor, or EGFR), KRAS^{G12C} inhibitors, and an ERK inhibitor as well as in combination with a PD-1 inhibitor. Sanofi, our SHP2 collaboration partner, will conduct the planned Phase 1 study evaluating RMC-4630 in combination with a PD-1 inhibitor.

In March 2020, the Pancreatic Cancer Collective (a strategic partnership between Lustgarten Foundation and Stand Up To Cancer) announced that it had awarded funding to the Netherlands Cancer Institute, or the NKI, for its study using our SHP2 inhibitor, RMC-4630 in combination with an investigational ERK inhibitor (LY3214996) in patients with pancreatic cancer. We plan to provide RMC-4630 to support this investigator sponsored study.

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Although we are at an early stage of clinical testing and product candidate development, we believe RMC-4630 is well-positioned to become the backbone of targeted therapy combinations for the treatment of various RAS-dependent tumors. Under our collaboration with Sanofi on our SHP2 program, we have a 50-50 profit share and a co-promote right in the United States and are eligible to receive royalties on net sales outside of the United States. Sanofi is responsible for reimbursing substantially all of our research costs and all of our development costs for the SHP2 program.

We are also developing a portfolio of what we believe to be the first potent, selective and cell-active inhibitors of mutant RAS(ON) proteins. Historically, direct inhibition of any RAS protein has been challenging due to a lack of tractable, or “druggable,” binding pockets. Recently, selective inhibitors of inactive, GDP-bound forms of RAS, or RAS(OFF), have demonstrated encouraging preliminary anti-tumor effects and thus provide clinical validation for targeting mutant RAS in cancer. Our small molecule inhibitors of mutant RAS(ON) are derived from our proprietary tri-complex technology platform, which enables us to target proteins lacking intrinsic drug binding sites by inducing new druggable pockets. Initially, we will prioritize four mutant RAS(ON) targets—KRAS^{G12C}, KRAS^{G13C}, KRAS^{G12D} and NRAS^{G12C}—and expect to nominate our first development candidate in 2020. We plan to evaluate our RAS(ON) inhibitors alone and in combination with other drugs and investigational new drugs, particularly in-pathway agents. We believe that targeted inhibition of various oncogenic RAS(ON) mutants represents a highly differentiated approach for treating the large population of patients with diverse RAS mutations, including non-small cell lung cancer, or NSCLC, colorectal, pancreatic and other cancers.

We have two preclinical programs targeting other key nodes in the RAS and mTOR signaling pathways. Our program targeting SOS1, a protein that plays a key role in converting RAS(OFF) to RAS(ON) in cells, is currently in lead optimization stage. In addition, our preclinical development candidate, RMC-5552, is designed to selectively and deeply inhibit mTORC1, thereby preventing phosphorylation and inactivation of 4EBP1, a downstream protein in the mTOR signaling pathway that normally suppresses expression of certain oncogenes such as C-MYC. mTORC1-selective inhibitors from our proprietary series, including RMC-5552, have recently been shown to have combinatorial activity with KRAS^{G12C} inhibitors in preclinical models of KRAS^{G12C} lung and colon cancer, suggesting that RMC-5552 is a significant and rational addition to our portfolio of RAS pathway inhibitors. We advanced RMC-5552 into IND-enabling development in June 2019.

Our management team has significant experience in oncology and in progressing products from early stage research to clinical trials, and ultimately to regulatory approval and commercialization. Dr. Steve Kelsey, our President of Research and Development, was previously President of Onkaido Therapeutics, a Moderna venture focused on oncology mRNA therapeutics, and has held senior positions at Medivation, Geron and Genentech, where he played a significant role in the development of Perjeta, Kadcyla and Erivedge. Our President and Chief Executive Officer, Dr. Mark Goldsmith, served as Chief Executive Officer of Constellation Pharmaceuticals, where he led the creation of its oncology pipeline and drove the development of a strategic alliance with Genentech. He also has led four other companies spanning early discovery through development, including Global Blood Therapeutics, where he led the discovery and early development of voxelotor.

Our company was founded and continues to be supported by three world-class scientific advisors: Dr. Kevan Shokat (Professor and Chair of the Department of Cellular and Molecular Pharmacology at University of California, San Francisco, Professor of Chemistry at the University of California, Berkeley and an investigator at the Howard Hughes Medical Institute), Dr. Martin Burke (Professor of Chemistry at the University of Illinois at Urbana-Champaign) and Dr. Michael Fischbach (Associate Professor in the Department of Bioengineering at Stanford University and a Stanford ChEM-H Institute Scholar). Dr. Shokat is widely recognized for his seminal contributions to the field of kinase biology, using chemistry, protein engineering and genetic tools to pioneer novel therapeutic approaches to target key signaling pathways in cancer. He led the discovery of the first KRAS^{G12C}(OFF) inhibitor.

Our strategy

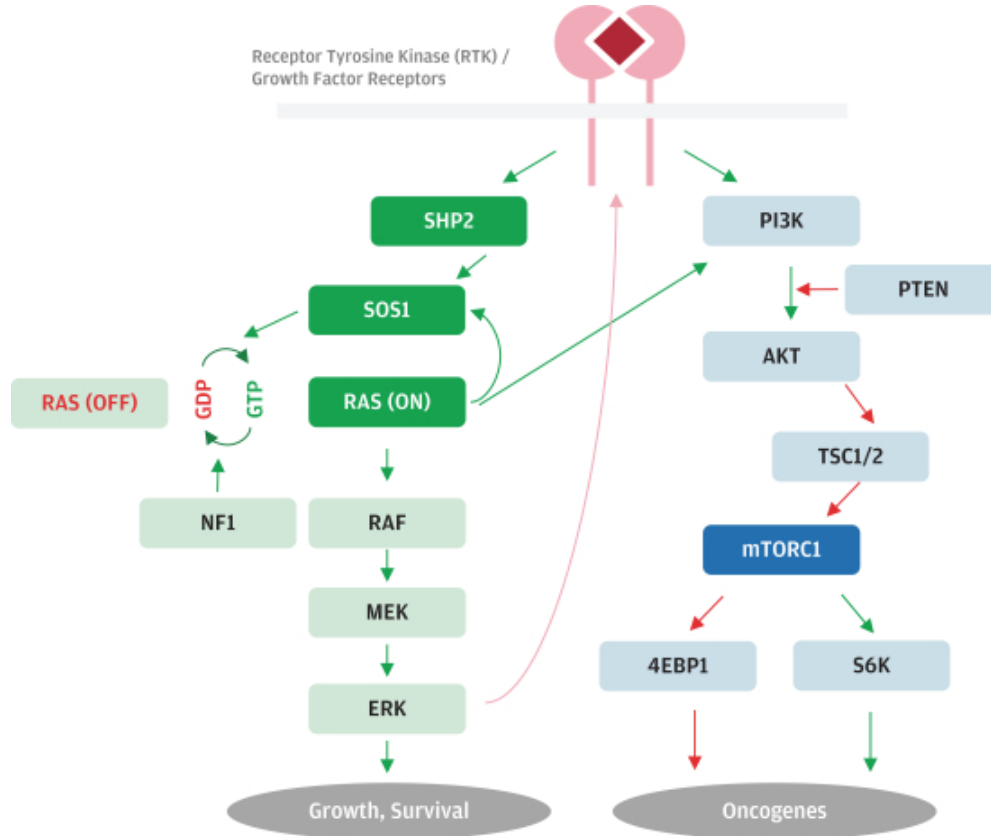
Our goal is to develop novel targeted therapies to outsmart cancer for the benefit of patients. We plan to pursue the following strategies:

- **Deploy our innovation engine against frontier oncology targets.** We use our chemical biology and cancer pharmacology know-how, structure-based drug discovery capabilities, and precision medicine approach to discover and develop compounds designed to overcome the complex molecular circuitry of cancer. We focus on a cohesive set of genetically defined targets in the RAS signaling pathway to create compounds that may be used alone and in combination with other targeted therapies. We evaluate in-pathway proprietary mechanism-based combination therapies and innovative dosing paradigms. Collectively, these are designed to maximize the depth and durability of clinical benefit and improve the lives of patients with cancer.
- **Establish our proprietary SHP2 inhibitor, RMC-4630, as the backbone of targeted therapy combinations for the treatment of RAS-dependent tumors.** As SHP2 is a convergent node within the oncogenic RAS-signaling pathway, we plan to evaluate RMC-4630 in combination with other in-pathway agents targeting RTK (initially EGFR), and KRAS^{G12C}. We have initiated a Phase 1b/2 trial of RMC-4630 with cobimetinib (a MEK inhibitor) and we plan to evaluate RMC-4630 in combination with osimertinib (an EGFR inhibitor). A Phase 1b study of RMC-4630 in combination with sotorasib, a KRAS^{G12C}(OFF) inhibitor is being conducted by Amgen, and we expect to subsequently study RMC-4630 in combination with our proprietary KRAS^{G12C}(ON) inhibitor once a clinical candidate has been selected for development. In March 2020, the NCI announced its intention to sponsor the SHERPA (SHP2 and ERK inhibitors in Pancreatic Cancer) study using our SHP2 inhibitor, RMC-4630. As many patients with tumors carrying mutations that are potentially SHP2-dependent are currently treated with immune checkpoint inhibitors, we also plan to study RMC-4630 in combination with a PD-1 inhibitor.
- **Pioneer mutant selective RAS(ON) inhibition across multiple genetically defined cancers.** There are dozens of RAS mutants that have been implicated as molecular drivers of cancer. We are developing a pipeline of small molecules targeting multiple oncogenic forms of RAS(ON) that are derived from our proprietary tri-complex technology platform. Initially, we will prioritize four mutant RAS(ON) targets—KRAS^{G12C}, KRAS^{G13C}, KRAS^{G12D} and NRAS^{G12C}—and expect to nominate our first development candidate in 2020. We plan to evaluate our RAS(ON) inhibitors alone and in combination with other drugs and investigational new drugs, particularly in-pathway agents. We believe that targeted inhibition of various oncogenic RAS(ON) mutants represents a highly differentiated approach for treating the large population of patients with diverse RAS mutations, including NSCLC, colorectal, pancreatic and other cancers.
- **Maximize the global value of our programs by continuing to execute synergistic and value-creating transactions.** We have the organizational capabilities and resources to enable us to continue to complete value-creating transactions, such as our collaboration with Sanofi on SHP2 and our acquisition of Warp Drive. In the future, we may enter into other collaborations where we believe there is an opportunity to accelerate the development and commercialization of our product candidates while allowing us to retain meaningful rights in major markets. We may also seek to acquire or in-license product candidates or technologies opportunistically that are synergistic with our drug discovery and development efforts.
- **Maintain our culture of tireless commitment to patients.** As we grow our business, we will continue to apply transformative science in the development of novel targeted therapies for patients suffering from cancers with limited therapeutic options. To accomplish this, we intend to continue building our team of qualified individuals who share our commitment to collaboration and scientific rigor in the development of novel therapies to outsmart cancer and improve the lives of patients.

Our opportunity: unmet needs in cancers with driver mutations in notorious growth and survival pathways

Background

The RAS and mTOR signaling cascades are among the most frequently exploited by human cancers. Cancer cells often carry mutations in proteins in these pathways that subvert normal cell growth and survival by causing excessive or aberrant signal transduction. These proteins can be directly or indirectly involved in signal transduction. For example, many tumors of different types exhibit excessive activation of the RAS signaling cascade as a result of mutations in RTKs, RAS, NF1 and/or RAF.



We have built a portfolio of compounds that inhibit select signaling nodes within the RAS and mTOR pathways. To date, our discovery and development efforts have focused on SHP2, RAS, SOS1 and mTORC1 (these targets are shaded dark green or blue in the figure above).

SHP2

SHP2 is a protein tyrosine phosphatase that plays a critical role in the transduction of intracellular signals downstream of a wide variety of RTK growth factor receptors to promote cell survival and growth. SHP2 acts as a central signaling node that regulates growth signals within normal cells and, in certain circumstances, cancer cells. Some mutant forms of RAS, such as KRAS^{G12C} and KRAS^{G12A}, exert their oncogenic effects by amplifying or exaggerating normal RTK-mediated growth signals transmitted via SHP2, and as a result they can be

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suppressed by inhibiting SHP2. There are other cancer-causing mutations that result in, or are dependent upon, activation of wild-type RAS and are likewise dependent on SHP2, including amplification of wild-type RAS or mutations in the gene encoding the GTPase-activating protein (GAP) neurofibromin 1 (NF1) which reduce activity of NF1 (so called NF1 loss-of-function or NF1^{LOF}), and class 3 mutations in the downstream effector BRAF (BRAF^{Class3}).

RAS

RAS proteins drive normal cell proliferation, differentiation and survival in response to growth factors acting through RTKs, and they can also be direct drivers of cancer. Normally RAS proteins cycle between an inactive form (RAS(OFF)), which is bound to GDP and unable to transmit signals, and an active conformation (RAS(ON)), which is induced upon binding GTP in response to growth factor receptor stimulation, causing it to become competent to interact physically with downstream effector proteins such as RAF. The magnitude of cell signals transmitted by the RAS activation cycle is proportional to the intracellular level of RAS(ON). In a healthy, normal cell RAS(ON) represents a small fraction of the total RAS pool within a cell. Signals arising from RTKs upstream of the RAS cycle act through SHP2 to promote the substitution of GTP for GDP in association with RAS, thereby increasing RAS(ON) levels. In cancers with abnormally elevated RTK activity, increased signaling via the RAS activation cycle is a major driver of tumor cell growth. Likewise, oncogenic mutations of RAS itself result in a significant slowing of the enzymatic conversion of RAS-bound GTP to GDP and thus drive cancer by raising RAS(ON) significantly above normal levels. In some cells harboring a KRAS^{G12C} mutation, 80% or more of cellular KRAS^{G12C} is in the GTP-bound state (RAS(ON)), representing a >15-fold increase compared to wild-type KRAS. As a general principle, RAS-dependent cancer cells exploit a high level of RAS(ON) for continued survival and growth.

SOS1

SOS1 is a member of a family of proteins that activate RAS. SOS1 directly activates RAS proteins by promoting the release of tightly bound GDP and facilitating the binding of GTP, which is present at a much higher intracellular concentrations than GDP, to generate RAS(ON). SOS1 itself is activated by RAS through the binding of RAS(ON) to an allosteric site on the SOS1 protein. As a result, there is a positive feedback loop between SOS1 and RAS that increases RAS signaling. The activation of RAS by SOS1 is 'processive'; that is, once a single molecule of SOS1 is activated it can sequentially activate multiple RAS molecules until it eventually becomes inactive.

4EBP1/mTORC1

mTORC1 and mTORC2 are large protein complexes that share mTOR kinase but contain distinct additional components and cellular functions. mTORC1 is a critical regulator of metabolism, growth and proliferation within cells, including cancer cells. Two of the main substrates of mTORC1 are eukaryotic initiation factor 4E-binding protein 1 (4EBP1) and ribosomal S6 kinase (S6K). Under resting conditions non-phosphorylated 4EBP1 functions as a suppressor of the translation of proteins that are required for cell growth, proliferation and survival. Phosphorylation of 4EBP1 by activated mTORC1 inhibits this suppressive regulatory function and thereby upregulates translation of these proteins. One of the most important proteins regulated by 4EBP1 is the oncogenic protein C-MYC, which for many years has been thought to be central to cancer cell growth and survival. The abnormal activation of mTORC1, and subsequent inactivation of the tumor suppressor 4EBP1, is a mechanism that is frequently harnessed by cancer cells to gain a growth and proliferation advantage over normal cells. A number of upstream proteins in the mTOR signaling pathway that regulate mTORC1 activity are frequently mutated, or deleted, in cancer cells, resulting in increased activation of mTORC1 and upregulation of translation; these targets of mutation include PTEN, PI3 kinase (PI3K) and hamartin (TSC1) and tuberlin (TSC2).

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RAS mutant epidemiology in the United States

Mutations in RAS proteins account for approximately 30% of all human cancers in the United States, many of which are fatal. Diverse oncogenic RAS mutations in three different RAS isoforms (KRAS, NRAS and HRAS) drive distinct human cancers. KRAS mutations are commonly found in NSCLC and account for approximately 85% of RAS-mutant cancers. NRAS mutations are commonly found in melanoma and account for approximately 11% of RAS-mutant cancers. HRAS mutations are commonly found in bladder cancer and account for 4% of RAS-mutant cancers. The table below summarizes the frequency of RAS cancer mutations in the United States. There continues to be a high unmet medical need for patients bearing tumors with these mutations. We believe our programs, including our SHP2, RAS and SOS1 inhibitors, may be useful in addressing this unmet medical need.

Projected number of new cases in 2019 in the United States (frequency % shown in parentheses below)

Histotype	Projected total new cases in 2019 [†]	KRAS G12C [‡]	KRAS G12D [‡]	KRAS G13C [‡]	KRAS G12A [‡]	NRAS G12C [‡]	NF1 (LOF) [‡]	BRAF Class3 [‡]	KRAS Amp [‡]
NSCLC* all	194,000	21,340 (11)	7,760 (4)	1,940 (1)	3,880 (2)	-	11,640 (6)	1,940 (1)	7,760 (4)
NSCLC* adeno only	91,000	12,740 (14)	4,550 (5)	910 (1)	2,730 (3)	-	4,550 (5)	910 (1)	2,730 (3)
Colorectal	145,000	5,800 (4)	21,750 (15)	435 (0.3)	2,900 (2)	290 (0.2)	4,350 (3)	1,450 (1)	1,450 (1)
Pancreatic	56,000	1,120 (2)	19,600 (35)	56 (0.1)	280 (0.5)	-	560 (1)	168 (0.3)	1,680 (3)
AML*	21,000	84 (0.4)	210 (1)	-	210 (1)	210 (1)	630 (3)	42 (0.2)	21 (0.1)
Uterine	61,000	610 (1)	1,830 (3)	244 (0.4)	1,220 (2)	61 (0.1)	2,440 (4)	305 (0.5)	1,830 (3)
Others	Melanoma: 96k Stomach: 28k	Melanoma 96 (0.1)	Melanoma 192 (0.2)	Stomach 56 (0.2)	Melanoma 96 (0.1)	Melanoma 192 (0.2)	Melanoma 12,480 (13)	Melanoma 2,880 (3)	Melanoma 960 (1)

(*) NSCLC = Non-small cell lung cancer; Adeno = adenocarcinoma; AML = Acute myeloid leukemia.

(†) Data are based on projections from the National Cancer Institute’s SEER Program for new cases of lung cancer, colorectal cancer, pancreatic cancer, AML and other cancers in 2019 and estimates from the American Cancer Society of the incidence of NSCLC and adenocarcinoma in lung cancer cases.

(‡) Reflects our estimate of projected number of cases in 2019 by RAS protein mutation for each cancer histotype indicated. Estimated frequency percentages (shown in parentheses) of RAS protein mutation in applicable histotype are based on data obtained from Foundation Medicine, Inc., applied to data described in footnote † above.

Limitations of approved drugs treating RAS-dependent cancers and our opportunity

A major goal in contemporary oncology treatment is to replace relatively unselective chemotherapy regimens—which in many cases remain the standard of care today but provide only partial benefit with many side effects—with more effective and better tolerated targeted therapeutic options. Targeted therapies directed against RAS-dependent cancers, which include drugs that inhibit RTKs, RAF and MEK, have been approved for use in lung cancer, melanoma and colorectal cancer. These targeted therapies have shown the capacity to drive deeper and more durable responses than conventional chemotherapy regimens while minimizing unwanted side effects and damage to normal tissues.

Two treatment gaps remain in RAS-dependent cancers. First, several oncogenic proteins are not addressed by current targeted therapies. Second, cancers driven by oncogenic proteins that are addressed by current targeted therapies often progress in the face of drug therapy due to adaptive resistance mechanisms.

Specific examples of *frontier* cancer drivers are RAS, NF1, and selected RAF mutants (BRAF^{Class3}). Historically, direct inhibition of any RAS protein has been challenging due to a lack of tractable, or “druggable,” binding

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pockets. Recently reported initial clinical results from two RAS(OFF) inhibitors targeting mutant KRAS^{G12C} suggest significant clinical benefit and provide strong pharmacologic validation of this oncoprotein as a cancer driver. These results, along with other preclinical data, provide a compelling basis for our commitment to targeting oncogenic mutant forms of RAS(ON). We are using our innovation engine to develop a portfolio of mutant-selective RAS(ON) inhibitors and, initially, we will prioritize four mutant RAS(ON) targets—KRAS^{G12C}, KRAS^{G13C}, KRAS^{G12D} and NRAS^{G12C}.

A common source of treatment failure with existing targeted therapies is that cancer cells exhibiting “oncogene addiction” exploit cell signaling circuitry to bypass the drug’s effect and sustain growth and survival. This phenomenon is particularly well recognized in RAS-dependent cancers, and may be especially active in certain tumor histotypes, making them less sensitive to a drug from the outset and/or more likely to progress over time. Certain RAS-dependent cancers have been treated with two RAS pathway targeted agents to achieve combinatorial benefit by attenuating adaptive resistance mechanisms. For example, melanomas driven by BRAF^{Class1} mutations can be treated with a combination of a BRAF inhibitor and a MEK inhibitor. SHP2 is believed to be a central node that can be targeted to disrupt bypass signaling pathways that may involve activation of multiple RTKs. Therefore, although we are at an early stage of clinical testing and product candidate development, we believe RMC-4630, a potent and selective inhibitor of SHP2, is well positioned to become the backbone of targeted therapy combinations for the treatment of various RAS-dependent tumors, and plan to explore this paradigm in our ongoing RMC-4630 clinical program.

We are using our innovation engine to develop novel targeted therapies and combination regimens to address these treatment gaps.

Our innovation engine

We have built an innovation engine that enables us to discover and develop novel targeted therapies for elusive high-value *frontier* cancer targets with particular focus on a cohesive set of disease targets within notorious growth and survival pathways. This engine consists of three complementary drivers:

- Deep **chemical biology and cancer pharmacology know-how**, including assays and proprietary tool compounds, to define the critical vulnerabilities of “frontier” RAS and mTOR pathway targets and associated signaling circuits in cancer cells;
- Sophisticated **structure-based drug discovery capabilities**, including proven **access to complex chemical space**, to create drug candidates tailored to unconventional binding sites on elusive cancer targets; and
- Astute **precision medicine approach**, embracing patient selection and innovative single agent and combination drug regimens, to translate our preclinical insights into clinical benefit for patients with genetically-defined cancers that are addicted to these pathways.

Our chemical biology and cancer pharmacology know-how

We test our inhibitors across a diverse set of human cancer cell and patient-derived *in vitro* and/or *in vivo* models of cancer. This is complemented by targeted implementation of bioinformatics and functional genomics. The biological insights we generate help us to unravel the complex molecular circuitry in human cancers. We also explore mechanisms of adaptive resistance that RAS-addicted cancer cells use to circumvent inhibition of the pathway, and develop innovative mechanism-based dosing paradigms and rational in-pathway combinations with our proprietary compounds and/or other agents. We evaluate such dosing and combination approaches in our preclinical *in vitro* and *in vivo* models to define their pharmacologic opportunities and limitations, and to prioritize therapeutic strategies for translation to the clinic.

Our structure-based drug discovery capabilities

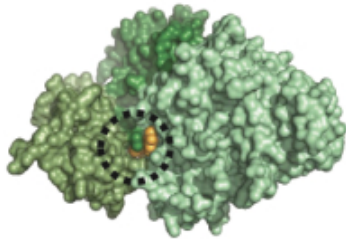
We enlist various technologies and capabilities that give us chemical access to challenging sites that are generally not accessible using conventional small molecule drug discovery approaches. For each target, we consider the specific structural, physico-chemical, functional and dynamic properties of the target and deploy the approach(es) that appears most likely to yield viable development candidates. In some instances the compounds we discover and develop are small molecules (e.g., less than 500 mw) with properties that generally satisfy conventional pharmaceutical "Rule of 5" criteria, while in other cases, they are larger (e.g., 500-1000 mw) "Beyond Rule of 5" compounds. In either case, we use various structure-based design tools to discover the initial chemical matter, drive optimization using iterative medicinal chemistry, and generate structure-activity and structure-property relationships to identify development candidates. In order to prosecute effective medicinal chemistry campaigns within complex chemical space, we use our deep experience and make the necessary investments to design and develop scalable modular chemical synthesis, purification and analytical methods for selected scaffolds to routinely and efficiently analogue our "Beyond Rule of 5" chemical series.

Although we are at an early stage of clinical testing and product candidate development, we believe our differentiated chemical approaches to discovering inhibitors for challenging *frontier* cancer targets is exemplified by our current portfolio. Each of our current programs takes advantage of allosteric regulation to inhibit the target of interest by exploiting one or more of three distinct mechanisms. We use the term allosteric inhibitors to describe those that "act at a distance," meaning that the inhibitory effect occurs at a protein site or domain distinct from the compound's binding site.

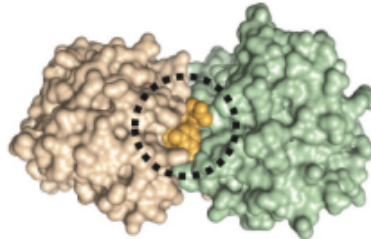
- i) **Intra-Molecular Allosteric Inhibitors:** Our SHP2 inhibitors, including RMC-4630, act by binding to a site in the protein that is distinct from the catalytic "active site" but nonetheless inhibit the phosphatase activity of SHP2. The inhibitors bind to a pocket within SHP2 that is formed when the protein is folded back onto itself in its basal, "autoinhibited" state; by binding to this pocket, these compounds stabilize the inactive conformation of SHP2 and therefore inhibit its overall function. We refer to this mechanism as "intra-molecular allostery" since it involves inhibitory actions entirely within the target protein itself. RMC-4630 is a traditional "Rule of 5" compound.
- ii) **Tri-Complex Inhibitors:** Our targeted mutant RAS(ON) portfolio takes advantage of our proprietary tri-complex technology that enables us to discover small molecule inhibitors of targets lacking intrinsic drug binding sites by inducing new druggable pockets. Our RAS inhibitors induce a new binding pocket on RAS(ON) by driving formation of a high affinity ternary complex (tri-complex) between the mutant RAS protein and a widely expressed cytosolic protein called a chaperone (e.g., FKBP12 or cyclophilin A). The inhibitory effect on RAS is mediated by steric occlusion of the interaction site between the mutant RAS and downstream effector molecules, such as RAF, which are required for propagating the oncogenic signal. We refer to this mechanism as "inter-molecular allostery" since it involves indirect inhibitory effects of a second protein (the chaperone) on the target in the presence of our tri-complex inhibitors. Our RAS(ON) inhibitors, which are inspired by natural products that act through this type of mechanism, are "Beyond Rule of 5" compounds.
- iii) **Bi-Steric Inhibitors:** Our mTORC1 inhibitors comprise two pharmacophores in a single compound. One pharmacophore binds to the well-known FRB (FKBP12-rapamycin binding) site on mTORC1 and the other binds to the mTOR kinase active site. As a result of these two binding interactions, such compounds exhibit two biologically useful features: (1) selectivity for mTORC1 over mTORC2, which is characteristic of the natural compound rapamycin, and (2) deep inhibition of mTORC1, which is characteristic of known active site inhibitors. These properties enable selective inhibition of phosphorylation of mTORC1 substrates, including 4EBP1. We refer to this type of inhibition as a "bi-steric mode." These mTORC1 inhibitors, which are inspired by natural products, are "Beyond Rule of 5" compounds.

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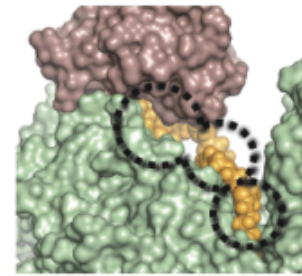
SHP2: Intra-Molecular Allosteric



RAS: Tri-Complex



mTORC1: Bi-Steric

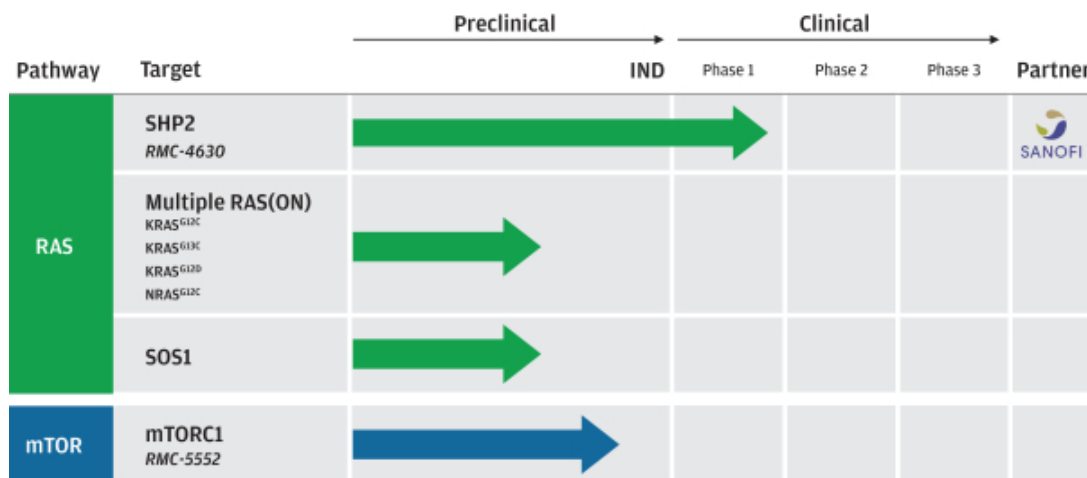


Our precision medicine approach

We interrogate the biology of different cancers and their associated mutational drivers to help inform patient selection, therapeutic treatment regimens, and appropriate outcome measures. To identify patient subsets that may benefit most from our treatment strategies, we use genomics, transcriptomics and proteomics data from human tumor samples and/or broad panels of human cancer cell lines. We also pursue development of drug combinations where combinatorial benefits are predicted and confirmed in preclinical models. Innovative, mechanism-based dosing paradigms are explored for each combination and refined using pharmacokinetic and pharmacodynamic modeling techniques and sophisticated continuous reassessment dosing methodology. We also identify and monitor pharmacodynamic biomarkers and surrogates of clinical activity to help measure target inhibition.

Our pipeline

We are using our innovation engine to develop a deep pipeline of novel targeted therapies to inhibit elusive, high-value *frontier* targets within the notorious RAS and mTOR signaling pathways. Our pipeline includes one product candidate that is in clinical development and all of our other programs are in the preclinical stage. Under our collaboration with Sanofi on our SHP2 program, we have a 50-50 profit share and a co-promote right in the United States and are eligible to receive royalties on net sales outside of the United States. Sanofi is responsible for reimbursing substantially all of our research costs and all of our development costs for the SHP2 program. For all other programs, we retain worldwide commercial rights.



Our SHP2 inhibitor, RMC-4630

Overview

Our most advanced product candidate, RMC-4630, is a potent and selective inhibitor of SHP2, based on preclinical evidence described in this prospectus. SHP2 is a protein that plays a central role in modulating cell survival and growth by transmitting signals from upstream RTKs to RAS. In collaboration with Sanofi, we are evaluating RMC-4630 in a multi-cohort Phase 1/2 clinical program, which includes:

- our ongoing Phase 1 study of RMC-4630 as monotherapy in patients with advanced cancers, including those with tumors harboring genetically defined mutations in the RAS signaling pathway,
- our ongoing Phase 1b/2 study of RMC-4630 in combination with the MEK inhibitor cobimetinib. Based on our own data, and supported by observations by others, we are evaluating intermittent dosing schedules in our clinical program to allow us to maximize dose intensity in order to achieve the greatest depth of response, and
- Amgen's ongoing Phase 1b study of RMC-4630 in combination with the KRAS^{G12C}(OFF) inhibitor sotorasib.

We also plan to explore the potential clinical benefit of RMC-4630 in combination with other in-pathway agents targeting EGFR (initially with osimertinib), KRAS^{G12C} and in combination with a PD-1 inhibitor. Sanofi, our SHP2 collaboration partner, will conduct the planned Phase 1 study evaluating RMC-4630 in combination with a PD-1 inhibitor. In March 2020, the Netherlands Cancer Institute announced plans to initiate a study combining RMC-4630 with an investigational ERK inhibitor in patients with pancreatic cancer in the second half of 2020. We plan to provide RMC-4630 to support this investigator sponsored study.

Although we are at an early stage of clinical testing and product candidate development, we believe RMC-4630 is well-positioned to become the backbone of targeted therapy combinations for the treatment of various RAS-dependent tumors.

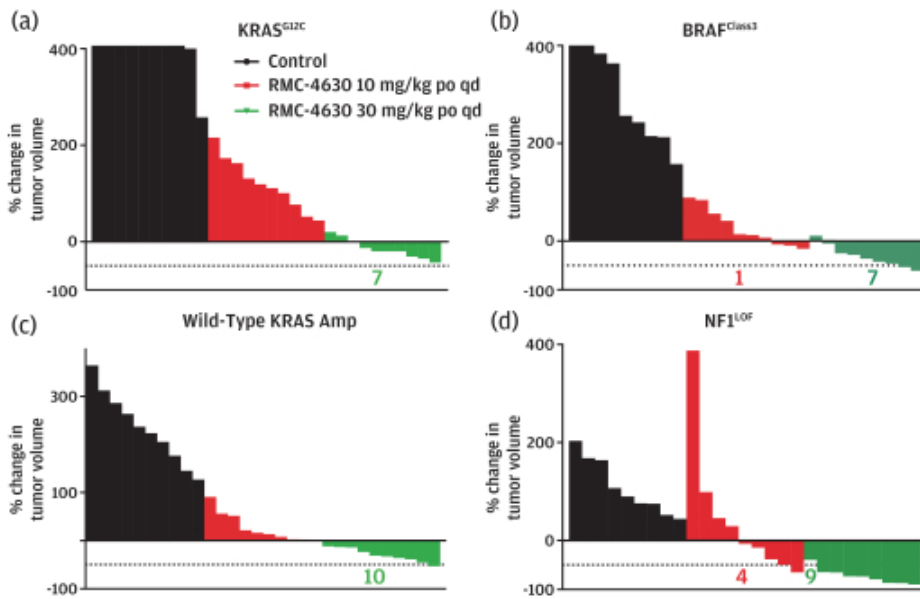
Preclinical profile of RMC-4630

RMC-4630 potently inhibits SHP2 phosphatase activity in a biochemical assay that monitored dephosphorylation of a probe substrate (IC₅₀ 1.29 nM, range 0.9 nM to 2.2 nM, number of experiments = 13) and SHP2 function in cellular assays, as measured by inhibition of ERK1/2 phosphorylation at Thr202/Tyr204, a read out for RAS pathway activation (IC₅₀ values of 14 nM in PC9^{EGFRex19del} cells, range 5.3 nM to 63 nM, number of experiments = 11; and 20 nM in NCI-H358 KRAS^{G12C} cells, range 14.5 nM to 27.5 nM, number of experiments = 4). In standard *in vitro* assays of target selectivity, no significant interaction with kinases or other phosphatases was observed. RMC-4630 (up to a test concentration of 10 μM) exhibited no inhibition of full length SHP1 phosphatase (number of experiments = 3), or the catalytic domains of SHP1 and thirteen other phosphatase enzymes (single experiment conducted in duplicate). RMC-4630 exhibited over 3,000-fold (range 7054 to >19,000, single experiment conducted in duplicate) selectivity for SHP2 (as measured by biochemical potency) over a panel of over 450 kinases (as measured by displacement of probe binding).

Preclinical anti-tumor activity

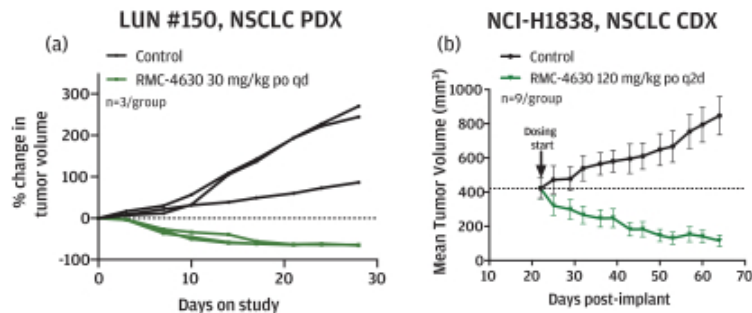
Consistent with the role of SHP2 as a regulator of the RAS cycle, we observed that RMC-4630 suppresses tumor growth in a dose-dependent manner in human cell-line or patient-derived preclinical xenograft models of tumors harboring KRAS^{G12C}, NF1^{LOF}, or BRAF^{Class3} mutations or wild-type KRAS amplifications (Figure 1a). Moreover, RMC-4630 at 30 mg/kg daily administered orally induced regression in some tumor models. The preclinical activity of RMC-4630 against tumors with NF1^{LOF} was confirmed in a series of patient-derived xenograft (PDX) models of tumors bearing NF1 mutations predicted to result in loss of function (LOF) (Figure 1b).

Figure 1a: RMC-4630 suppresses tumor growth in preclinical xenograft models of tumors harboring KRAS^{G12C}, NF1^{LOF}, or BRAF^{Class3} mutations or wild-type KRAS amplifications.



Daily oral administration (po qd) of RMC-4630 at 10 mg/kg (red) or 30 mg/kg (green) produces a dose-dependent inhibition of tumor growth in multiple solid human tumor cell line-derived or patient-derived xenograft (CDX or PDX, respectively) models bearing RAS pathway activating mutations of interest. All human xenograft models implanted in immune-deficient mice: (a) non-small cell lung cancer (NSCLC) PDX LUN#092 KRAS^{G12C}, (b) NSCLC BRAF^{Class3} PDX LUN#023 (BRAF^{D594N}), (c) gastric cancer PDX STO#332 wild-type KRAS amplification (KRAS Amp, copy number, CN = 4) and (d) NSCLC CDX NCI-H1838 NF1^{LOF} (NF1^{L184fs}). Control animals are shown in black. Data represent waterfall plots of individual end of study tumor responses, with tumor volume expressed as a percentage of initial tumor volume at time of study start (truncated at 400%). Each animal is represented as a separate bar (number of mice per group = 9 to 10). Numbers indicate number of regressions (defined as > 10% reduction in tumor volume from starting volume) in each group. Dotted line references 50% reduction in tumor volume. The duration of treatment with RMC-4630 or vehicle control was within a range of 30 days to 50 days across the four models.

Figure 1b: RMC-4630 causes tumor growth inhibition and regressions in diverse preclinical NF1^{LOF} models



- Anti-tumor effects in numerous NF1^{LOF} PDX models
 - Tumor growth inhibition in 62% (34/55) of models
 - 25% of responses were regressions
- Regressions with intermittent dosing in NF1^{LOF} CDX models

Anti-tumor activity of RMC-4630 in preclinical models of NSCLC tumors bearing mutations predicted to result in loss of function (LOF) of neurofibromin 1 (NF1) (NF1^{LOF}). Predicted LOF mutations include deletions, insertions, premature stops and truncations in the neurofibromin 1 gene. (a) Effect of daily oral administration (po qd) of RMC-4630 at 30 mg/kg (green) or vehicle control (black) on tumor growth in NSCLC LUN#0150 human PDX model (number of animals per group = 3). Graph shows tumor volume data for individual animals, expressed as a percentage of initial tumor volume at time of study start. The effects of

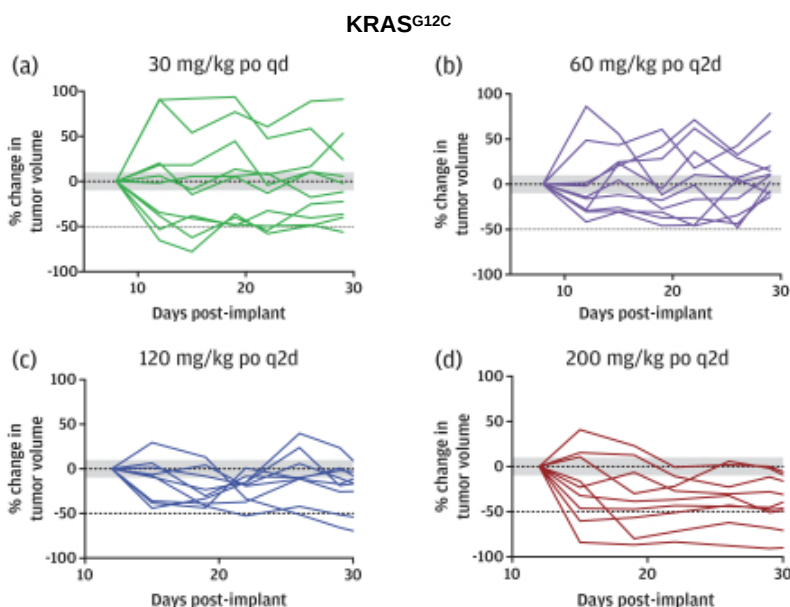
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RMC-4630 at 30 mg/kg po qd were evaluated across a total of 55 human PDX models of varying histotypes all with predicted NF1^{LOF}. Tumor growth inhibition was observed in 34/55 models (62%) and tumor regressions in 23/93 (25%) mice that had a response (93/166 mice). **(b)** Effect of intermittent, every other day, oral administration (po q2d) of RMC-4630 at 120 mg/kg (green) or vehicle control (black) on tumor growth in NSCLC NCI-H1838 human CDX model (number of animals per group = 9). Graph shows mean tumor volume data. Dotted line references baseline tumor volume. All dose regimens were well-tolerated.

Optimizing dosing and scheduling

Using an intermittent dosing schedule, which permits deep but discontinuous inhibition of the SHP2 target, significantly higher doses of RMC-4630 were tolerated than could be delivered with daily dosing. These higher doses of RMC-4630 led to increased tumor growth inhibition and resulted in more frequent and deeper tumor regressions (Figure 2).

Figure 2: Intermittent dose regimens of RMC-4630 produce deeper and more frequent tumor regressions than daily dosing at maximal tolerated dose in a preclinical xenograft model of NSCLC tumors harboring KRAS^{G12C} mutations.



Anti-tumor activity of daily (qd) and intermittent, every other day, (q2d) oral (po) dose regimens for RMC-4630 in NSCLC NCI-H358 KRAS^{G12C} cell line-derived xenograft model in mice. Graphs show tumor volume data for individual animals, expressed as a percentage of initial tumor volume at time of study start, for **(a)** 30 mg/kg qd, **(b)** 60 mg/kg q2d, **(c)** 120 mg/kg q2d and **(d)** 200 mg/kg q2d dose regimens (number of animals per group = 9 to 10). Changes in tumor volume of greater than 10% (grey zone) are considered significant. Dotted line references 50% reduction in tumor volume. All dose regimens were well-tolerated.

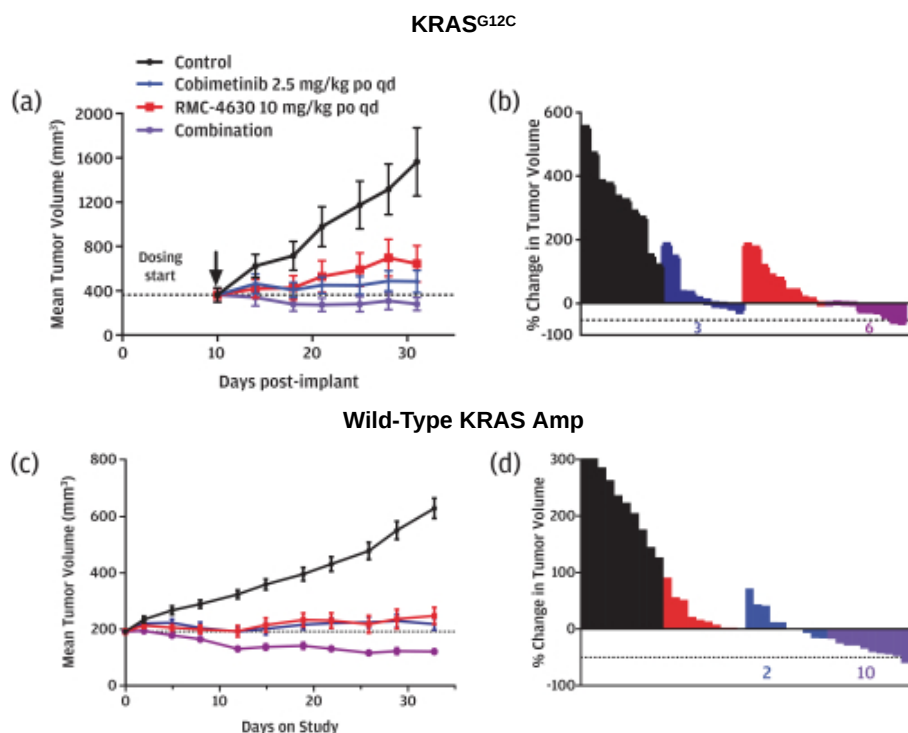
Rationale for combining with other targeted agents

Certain cancer treatments that inhibit components of the RAS signaling pathway are often unable to achieve the desired clinical effect as single agents due to the rapid development of adaptive resistance. These resistance mechanisms often involve hyperactivation of various RTKs that drive oncogenic signals via SHP2. Given that SHP2 is required for RAS signaling pathway activation by many RTKs, it might represent a viable target to limit potential resistance to other single-agent treatments. Inhibition of SHP2 in cell culture experiments abrogated RTK signaling and, in preclinical studies, RMC-4630 demonstrated combinatorial activity when given with other RAS signaling pathway inhibitors, such as MEK, KRAS^{G12C} or EGFR.

MEK inhibitors, such as cobimetinib, are approved for the treatment of certain types of melanoma but only in combination therapy. As single agents they have shown limited clinical effect, particularly in lung cancers carrying RAS mutations, which is believed to be due in part to adaptive resistance mechanisms.

In several preclinical tumor xenograft models either RMC-4630 or cobimetinib, dosed as single agents at doses lower than the maximally tolerated dose for each agent, inhibited tumor growth but induced few tumor regressions. However, the number and depth of tumor regressions was markedly increased upon treatment with a combination of these low-doses of RMC-4630 and cobimetinib (Figure 3).

Figure 3: Combination benefit for RMC-4630 and cobimetinib in preclinical xenograft models of tumors harboring KRAS^{G12C} mutations or wild-type KRAS amplifications.



Anti-tumor activity of RMC-4630 (10 mg/kg, red) and cobimetinib (2.5 mg/kg, blue) dosed daily by oral administration (po, qd) as single agents or in combination (purple) in (a and b) NSCLC CDX NCI-H358 KRAS^{G12C} and (c and d) gastric cancer PDX STO#332 wild-type KRAS amplification (KRAS Amp, CN = 4) xenograft models in mice. Data represent (a and c) mean tumor volume over time or (b and d) waterfall plots of individual end of study responses with tumor volume expressed as a percentage of initial tumor volume at time of study start (truncated at 300% in d). In (a) and (c) data represent mean and errors bars represent standard error of the mean. Each animal represented as a separate bar in (b and d). Number of animals per group = 10. Respective doses (in parentheses) of RMC-4630 (10 mg/kg) and cobimetinib (2.5 mg/kg) are lower than the corresponding maximally-tolerated dose for each agent. Numbers indicate number of regressions (defined as > 10% reduction in tumor volume from starting volume) in each group.

There are three important implications of these observations: first, the anti-tumor effects of RMC-4630 may be significantly greater in human cancers that are already predicted to be sensitive to SHP2 inhibition if RMC-4630 is combined with a MEK inhibitor. Second, the effects of the combination may be observed at doses or exposures of RMC-4630 or a MEK inhibitor that are significantly below the maximum tolerated dose for each agent. Third, there may be a higher probability of invoking tumor cell death with the combination, and thus seeing tumor regressions.

In addition, two of our academic collaborators have demonstrated that tumors with KRAS^{G12D} or KRAS^{G13D} mutations may be responsive to a SHP2 inhibitor combined with a MEK inhibitor. Based on their published

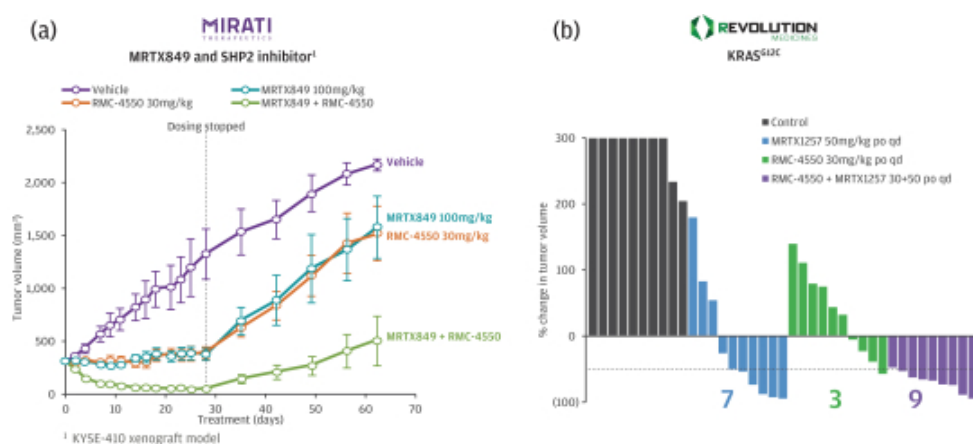
results, the RMC-4630 and MEK inhibitor combination may be active in some tumors with mutations that may not be sensitive to SHP2 inhibition alone.

The combination of RMC-4630 and cobimetinib has been relatively well tolerated in preclinical studies. We have also sought to maximize potent anti-tumor activity of RMC-4630, and reduce potential side effects, by deploying an intermittent dosing schedule.

An academic collaborator has presented preclinical data on the combination of a SHP2 inhibitor and an ERK inhibitor, providing rationale for the potential clinical evaluation of the combination.

Recently reported initial clinical results from two KRAS^{G12C}(OFF) inhibitors suggest significant clinical benefit and provide strong pharmacologic validation of this oncoprotein as a cancer driver. Preclinical studies have demonstrated that KRAS^{G12C}(OFF) inhibitors also cause a rapid increase in signaling through RTKs that are typically SHP2-dependent. Thus, the magnitude and durability of effect of an inhibitor of KRAS^{G12C}(OFF) may be significantly increased when combined with a SHP2 inhibitor that disrupts signaling from the activated RTKs. Recent data have demonstrated that a combination of our proprietary SHP2 inhibitor with KRAS^{G12C}(OFF) inhibitors can drive significant tumor regression in two distinct KRAS^{G12C} driven tumor models that exhibit only partial anti-tumor responses to either compound alone (Figure 4).

Figure 4: Combination benefit for SHP2 inhibitor and KRAS^{G12C}(OFF) inhibitor in preclinical xenograft models of tumors harboring KRAS^{G12C} mutations.



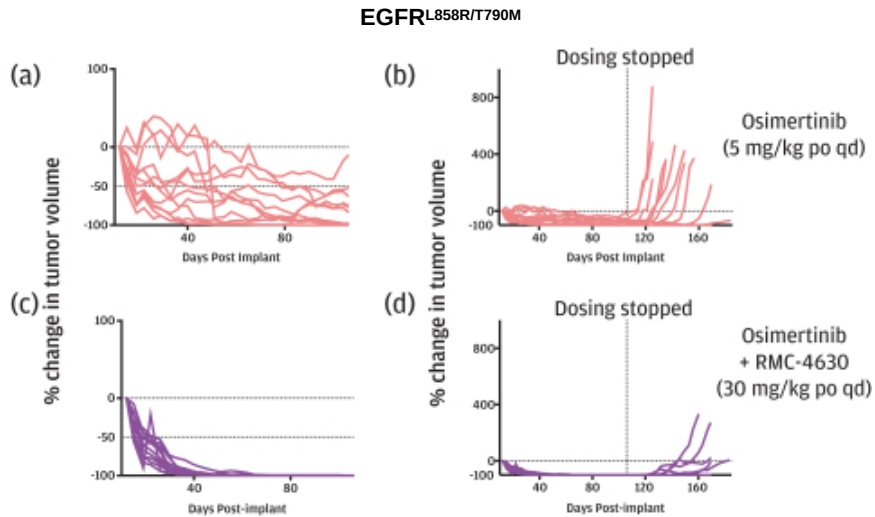
Anti-tumor activity of a representative SHP2 allosteric inhibitor (RMC-4550) and a KRAS^{G12C}(OFF) inhibitor (MRTX849 or MRTX1257) dosed daily by oral administration (po, qd) as single agents or in combination in (a) esophageal carcinoma KYSE-410 and (b) NSCLC NCI-H358 KRAS^{G12C} cell line-derived xenograft models in mice. Data represent (a) mean tumor volume over time or (b) waterfall plot of individual end of study responses, with tumor volume expressed as a percentage of initial tumor volume at time of study start (truncated at 300%). Data in panel (a) taken from an August 2019 Mirati corporate presentation; show evidence for tumor regressions, in addition to reduced rate of tumor regrowth after 'dosing stopped', for the SHP2 plus KRAS^{G12C}(OFF) inhibitor combination group relative to either single agent group. For our data in panel (b) each animal is represented as a separate bar (number of animals per group = 10). Numbers indicate number of regressions (> 10% reduction in tumor volume from starting volume) in each group. RMC-4550 is a potent and selective SHP2 allosteric inhibitor tool compound (see Nichols et al., 2018). MRTX849 is Mirati's KRAS^{G12C}(OFF) clinical candidate and MRTX1257 is a potent and selective KRAS^{G12C}(OFF) inhibitor tool compound.

In approximately 25% of NSCLC in North and South America, EGFR is mutated and drives tumor growth. EGFR inhibitors are used to treat these types of lung cancer, but emergence of resistance is a clinical problem. With recently approved EGFR inhibitors such as osimertinib (marketed as Tagrisso by AstraZeneca), emergent resistance is frequently due to mutation or amplification of signaling proteins other than EGFR. Similar to the adaptive resistance pathways activated by MEK inhibitors, several of these escape drivers have been shown to signal through SHP2.

RMC-4630 enhanced the anti-tumor activity of osimertinib in preclinical models of osimertinib-sensitive and osimertinib-resistant EGFR-mutant tumors (Figures 5 and 6). RMC-4630 accelerated and increased the magnitude

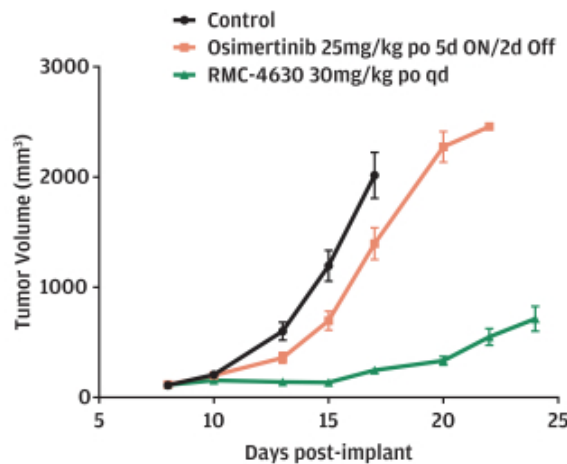
of tumor regression in an osimertinib-sensitive tumor and delayed and/or reduced tumor regrowth upon cessation of treatment in this model. RMC-4630 also inhibited tumor growth in a patient-derived tumor xenograft that had become resistant to osimertinib via amplification of the oncogene c-MET, an RTK that has been shown to drive some forms of cancer and that signals through SHP2. This suggests that, under circumstances where escape from osimertinib occurs via a SHP2-dependent mechanism, RMC-4630 may have clinical activity.

Figure 5: Combination benefit for RMC-4630 and the EGFR inhibitor, osimertinib, in an EGFR^{L858R/T790M} osimertinib-sensitive NSCLC xenograft model.



Anti-tumor activity of osimertinib (5 mg/kg) dosed daily by oral administration (po, qd) as a single agent (a and b) or in combination with RMC-4630 (30 mg/kg po, qd) (c and d) in NSCLC NCI-H1975 (EGFR^{L858R/T790M}) cell line-derived xenograft model in mice. Graphs show tumor volume data for individual animals, expressed as a percentage of initial tumor volume at time of study start (number of animals per group =12). Horizontal dotted lines reference the starting tumor volume (0%) and a 50% reduction in tumor volume. Vertical dotted line marks time at which dosing was stopped. Panels (a and c) show the same data as in (b and d) up to the time point of dosing cessation but on an expanded time scale.

Figure 6: RMC-4630 suppresses tumor growth in an osimertinib-resistant NSCLC patient-derived xenograft model (EGFR^{L858R/T790}/MET^{amplified}).



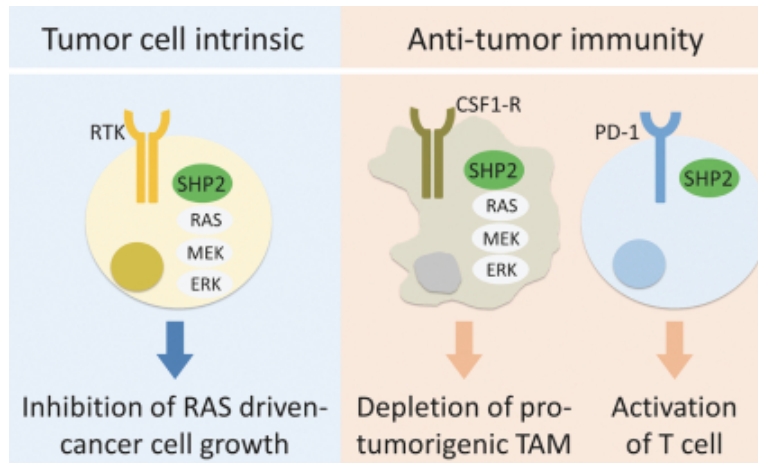
Daily oral administration of RMC-4630 (30 mg/kg po, qd) inhibits tumor growth in an osimertinib-resistant NSCLC patient-derived xenograft model (EGFR^{L858R/T790}/MET^{amplified}) wherein the EGFR^{T790M} allele was no longer detected and the patient tumor exhibited genomic amplification of the MET receptor tyrosine kinase. The human tumor xenograft model was implanted in immune deficient mice. Data represent mean and errors bars represent standard error of the mean. Number of animals per group = 10. Osimertinib 25 mg/kg, 5 days on/2 days off had no significant impact on tumor growth as anticipated.

Rationale for combining with immune checkpoint inhibitors

Immune checkpoint inhibitors, such as inhibitors of PD-1, have been useful against a variety of tumor types, including melanomas, breast and lung cancers, certain types of colon cancer and bladder cancers. It has been proposed in the scientific literature that SHP2 interacts with the PD-1 receptor and mediates at least part of its immune suppressive signals. We have observed that SHP2 inhibition phenocopies some of the effects of PD-1 blockade in certain *in vitro* and *in vivo* models, including activation of CD8+ T-cells.

In addition to these effects, we have also observed that SHP2 inhibition inhibits the viability of pro-tumorigenic (M2) macrophages *in vitro*, an effect not observed with PD-1 inhibitors. In the tumor microenvironment *in vivo*, SHP2 inhibition reduced the number of M2 macrophages while also promoting increases in the anti-tumor M1 macrophages population, effects not observed with checkpoint inhibitors. Therefore, RMC-4630 may increase the ability of the innate and adaptive arms of the immune system to control or even eradicate cancer cells. These findings point to the potential for a dual mechanism of action of SHP2 inhibitors with both tumor cell intrinsic and anti-tumor immunity effects (Figure 7a).

Figure 7a. SHP2 Inhibitor Promotes Anti-Tumor Responses via Effects on Innate and Adaptive Immunity

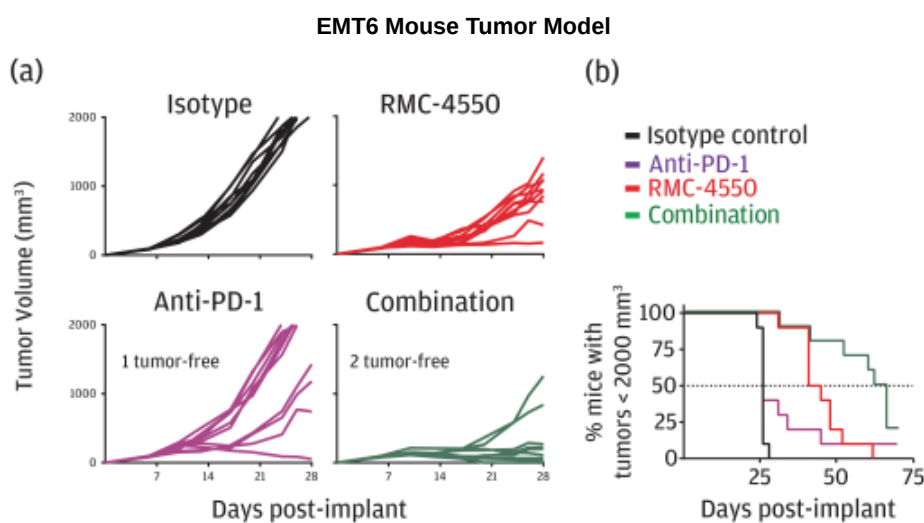


SHP2 is an established signaling node downstream of RTKs in the RAS growth and survival pathway and inhibition of SHP2 can block growth of cancer cells with certain oncogenic drivers in the RAS pathway. SHP2 also participates in signal transduction downstream of regulatory immunoreceptors. Inhibition of SHP2 drives anti-tumor immunity through modulation of both innate and adaptive mechanisms in preclinical models: direct and selective depletion of M2 pro-tumorigenic macrophages through attenuation of CSF-1R signaling and blockade of inhibitory (PD-1) signaling in CD8+T cells. Collectively, these mechanisms contribute to generate a less immunosuppressive environment and one that favors tumor cell elimination. In those cancers with aberrant RAS pathway activation, which are intrinsically sensitive to SHP2 inhibition, the ultimate impact on tumor cell growth may reflect integration of both the targeted tumor cell intrinsic and anti-tumor immunity mechanisms.

In models of cancer in immunocompetent mice, SHP2 inhibition activated the murine immune system to slow tumor growth, even in tumors that are not intrinsically sensitive to direct cellular effects of SHP2 inhibition. In preclinical models, the combination of a SHP2 inhibitor with an immune checkpoint inhibitor, such as a PD-1 inhibitor, occasionally induced an immune response that is sufficient for mice to 'reject' their tumors completely and elicit immunological memory.

Significant anti-tumor effects of SHP2 inhibition, both alone and in combination with PD-1 inhibition, were also observed in tumors intrinsically sensitive to SHP2 inhibition *in vitro* (Figure 7b). The combination produced deep and durable tumor growth inhibition, with complete tumor regressions and sustained immunological memory in some mice. A SHP2 inhibitor such as RMC-4630 may, therefore, elicit anti-tumor effects via two separate biologic mechanisms: targeted inhibition of RAS-dependent tumor growth, and liberation of anti-tumor immune responses by transformation of the tumor microenvironment.

Figure 7b: Anti-tumor effects of SHP2 inhibition alone and in combination with PD-1 checkpoint blockade in the EMT6 syngeneic model.



RMC-4550 (30 mg/kg) was administered daily by oral administration for the duration of the study starting at day 6 post-implant; anti-PD-1 (10 mg/kg) was administered every three days by intra-peritoneal administration, for a total of 7 doses starting at day 6 post-implant, or a combination of both was administered to EMT6 tumor bearing immunocompetent mice. Control animals received the isotype control for the anti-PD-1 antibody. Data represent (a) tumor growth of individual mice for each experimental group and (b) Kaplan-Meier curves showing percentage of animals with tumor burden < 2000 mm³ in each treatment group for the duration of the study. RMC-4550 is a potent and selective SHP2 allosteric inhibitor tool compound. Number of animals per group = 10.

Development strategy

In summary, preclinical research suggests that RMC-4630 has the potential to cause significant anti-tumor effects:

- In tumors harboring certain mutations of the RAS signaling pathway;
- When administered at high doses on an intermittent basis;
- When given in combination with other targeted anti-cancer agents such as inhibitors of MEK, EGFR or mutated KRAS, such as KRAS^{G12C}; and
- If both the direct effects of SHP2 inhibition on cancer cells with RAS pathway mutations and activation of the immune system occur concurrently, which may be heightened through combination with a PD-1 inhibitor.

Although we are at an early stage of clinical testing and product candidate development, we believe RMC-4630 is well-positioned to become the backbone of targeted therapy combinations for the treatment of various RAS-dependent tumors (Figure 8).

Figure 8

Tumors with RAS pathway mutations	Example	Near-term	Longer-term
Mutant-selective inhibitors available or in advanced clinical testing	KRAS ^{G12C}	RMC-4630 + KRAS ^{G12C} (OFF) inhibitor (AMG 510)	RMC-4630 + KRAS ^{G12C} (ON) inhibitor +/- Checkpoint inhibitor (PD-1)
	EGFR	RMC-4630 + EGFR inhibitor (osimertinib)	RMC-4630 + EGFR inhibitor (osimertinib)
Mutant-selective inhibitors unlikely to become available	NF1 ^{LOF} BRAF ^{Class3}	RMC-4630 + MEK inhibitor (cobimetinib)	RMC-4630 + MEK inhibitor (cobimetinib) +/- Checkpoint inhibitor (PD-1)

Phase 1/2 clinical program

In collaboration with Sanofi, we are evaluating RMC-4630 in a multi-cohort Phase 1/2 clinical program. This RMC-4630 Phase 1/2 program currently consists of three active clinical trials:

- RMC-4630-01, a Phase 1 study of RMC-4630 as a single agent,
- RMC-4630-02, a Phase 1b/2 study of RMC-4630 in combination with the MEK inhibitor cobimetinib, and
- A Phase 1b study of RMC-4630 in combination with the KRAS^{G12C}(OFF) inhibitor sotorasib, being conducted by Amgen as one arm of its CodeBreak 101 study.

RMC-4630-01 study of single agent RMC-4630 in patients with advanced solid tumors

RMC-4630-01 is a Phase 1 study in patients with advanced cancers, including those with tumors harboring genetically defined mutations in the RAS signaling pathway, that is evaluating the safety, pharmacokinetics and pharmacodynamic effects of RMC-4630 as a single agent under two different dose administration schedules: daily and twice weekly dosing. A preliminary evaluation of anti-tumor activity is also being made in patients who have tumors harboring mutations in the RAS pathway that are predicted to be sensitive to SHP2 inhibition, including KRAS^{G12C}, KRAS^{G12A}, NF1^{LOF}, and BRAF^{Class3} and others (e.g., KRAS^{amp}).

The RMC-4630-01 study has been designed to evaluate different schedules: a daily dosing schedule and two different intermittent dosing schedules (Day 1 and Day 4 of each week, and Day 1 and Day 2 of each week). The intermittent schedules were intended to achieve intermittent target coverage which, in preclinical models, was associated with similar or superior activity and better tolerability. The RMC-4630-01 trial is currently being conducted at 12 clinical study sites in the United States.

As of the data cut-off on May 4, 2020, we reported the following preliminary data from RMC-4630-01:

In RMC-4630-01, 87 patients had been enrolled and had received study drug and were evaluable for safety: 38 with the intermittent schedule and 49 with the daily schedule (Tables 1, 5 and 7).

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Dose escalation has been completed for the daily dosing schedule and for the intermittent weekly D1,D4 schedule. Dose escalation continues using the intermittent weekly D1,D2 schedule.

Preliminary data suggest improved tolerability of the intermittent dosing schedules versus daily dosing. Therefore, safety, tolerability and pharmacokinetic data for patients treated with the intermittent schedules are reported separately from patients treated with the daily schedule.

Interim safety and tolerability – intermittent dosing schedules

31 patients have been dosed with the intermittent weekly D1,D4 schedule and 7 patients have been dosed with the weekly D1,D2 schedule. Across both intermittent schedules 38 patients have been evaluated for safety after a median RMC-4630 exposure of 1.8 months (range 0.2-10.6 months). Demographic and baseline characteristics information is shown in Table 1.

Table 1: Demographics and baseline characteristics—intermittent schedule in RMC-4630-01 study.

	140 mg D1D4 (N=8)	200 mg D1D4 (N=18)	240 mg D1D4 (N=5)	200 mg D1D2 (N=4)	240 mg D1D2 (N=3)
Age, median (range)	63 (47-82)	66.5 (24-38)	65 (58-79)	59.5 (59-77)	64 (62-77)
Male (%)	4 (50.0%)	8 (44.4%)	1 (20.0%)	3 (75.0%)	1 (33.3%)
Cancer Type					
Lung (%)	5 (62.5%)	13 (72.2%)	3 (60.0%)	2 (50.0%)	2 (66.7%)
Colon and/or Rectal (%)	0	2 (11.1%)	1 (20.0%)	2 (50.0%)	1 (33.3%)
Other (%)	3 (37.5%)	3 (16.7%)	1 (20.0%)	0	0
ECOG performance status					
0	1 (12.5%)	5 (27.8%)	0	1 (25.0%)	1 (33.3%)
1	7 (87.5%)	13 (72.2%)	5 (100.0%)	3 (75.0%)	2 (66.7%)
Number of prior cancer therapies, median (range)	3.5 (2-8)	2.5 (1-9)	4 (1-5)	3.5 (2-9)	3 (2-3)

Data as of May 4, 2020.

The emerging safety profile of RMC-4630 when dosed on an intermittent schedule is consistent with the mechanistic effects of the product candidate on SHP2 and hence the RAS signaling cascade, including edema, gastrointestinal toxicity, reduced red cell production (low hemoglobin concentration and worsening of pre-existing anemia), reduced platelet production (thrombocytopenia), hypertension and fatigue. This safety profile was largely predictable from preclinical studies and clinical studies of other well-known inhibitors of this pathway.

Treatment-related adverse events, or related AEs, occurring in greater than or equal to 10% of patients are listed in Table 2. One grade 4 treatment-related AE of thrombocytopenia has been reported in a patient receiving 240 mg BIW D1D4. No related grade 5 AEs have been reported.

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Table 2: Related AEs occurring in ³ 10% of dosed patients by grade—intermittent schedule in RMC-4630-01 study.

All Intermittent (N=38)					
Preferred Term	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	15 (39.5%)	10 (26.3%)	3 (7.9%)	2 (5.3%)	0
Anemias (SMQ)*	10 (26.3%)	1 (2.6%)	5 (13.2%)	4 (10.5%)	0
Fatigue	10 (26.3%)	7 (18.4%)	2 (5.3%)	1 (2.6%)	0
Thrombocytopenias (SMQ)**	10 (26.3%)	3 (7.9%)	5 (13.2%)	1 (2.6%)	1 (2.6%)
RevMed Edemas (CMQ)***	8 (21.1%)	7 (18.4%)	1 (2.6%)	0	0
Nausea	7 (18.4%)	4 (10.5%)	1 (2.6%)	2 (5.3%)	0
Vomiting	6 (15.8%)	3 (7.9%)	1 (2.6%)	2 (5.3%)	0

Data as of May 4, 2020. Abbreviations: SMQ, Standardized MedDRA Query; CMQ, Customized MedDRA Query.

* Includes hemoglobin count decrease.

** Includes platelet decrease.

*** Consists of eyelid edema, face edema, generalized edema, lip edema, edema, edema peripheral, periorbital edema and peripheral swelling.

Four patients (11%) had serious adverse events, or SAEs, thought to be possibly or probably related to the study drug as assessed by the trial sponsor across all intermittent dosing cohorts. Three SAEs were reported among three patients receiving 200 mg D1D4 (Grade 3 abdominal distention, Grade 3 anemia, Grade 2 deep vein thrombosis, one patient each). Four SAEs were reported in one patient receiving 240 mg D1D4 (pleural effusion, pulmonary embolism, nausea, and vomiting, all Grade 3).

Three additional SAEs (cerebrovascular accident, multifocal pneumonia, and pleural effusion) were reported in which the investigator was unable to rule out an association with the study drug, but where the evidence for causality by RMC-4630 was absent or considered unlikely by the study sponsor. One patient presented symptoms five days after starting study drug where a total of two doses were administered. Patient had major risk factors for developing a cerebrovascular accident including underlying bladder cancer, pancreatic adenocarcinoma, recent major thromboembolic event of pulmonary embolism less than two months prior to start of study treatment, elderly age, history of coronary artery calcification, smoking and hypertension. A second patient had pneumonia which is not an expected event for RMC-4630. After taking two doses of study drug, patient was hospitalized due to suspicion of post-obstructive pneumonia which was later updated to multifocal pneumonia. No pathogens were identified from the infection work-up. Given the history of lung cancer, the sponsor considers this event unlikely related to RMC-4630. A third patient had NSCLC and a history of multiple pleural effusions (including prior to starting study treatment) with multiple thoracentesis performed. Given patient history and the rapid accumulation of pleural fluid after the drug was held, the sponsor believes that this event is most likely due to underlying disease progression and is unlikely related to RMC-4630. No grade 4 or 5 related SAEs have been reported in the intermittent cohort.

Overall, the D1,D2 weekly intermittent dosing schedule seems to be better tolerated than the weekly D1,D4 dosing schedule (Table 3) and the daily dosing schedule and yet permits an equivalent weekly dose intensity of RMC-4630.

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Table 3: Comparison of key safety/tolerability findings for three tolerated doses at three different schedules; daily, weekly intermittent D1D4 and weekly intermittent D1D2.

	60 mg Daily (N=18)	140 mg D1D4 (N=8)	200 mg D1D2 (N=4)
Grade 3 Related AEs	7 (38.9%)	4 (50.0%)	0
Grade 4 Related AEs	2* (11.1%)	0	0
AEs Leading to Study Drug Discontinuation/Dose Reduction	4 (22.2%)	1 (12.5%)	0

* Relatedness in this table is based on investigator assessment. One Grade 4 SAE of respiratory failure and one Grade 3 SAE of QTc prolongation (previously reported) were considered unlikely related to RMC-4630 by the sponsor.

Pharmacokinetics—intermittent dosing schedule

The pharmacokinetic profile of RMC-4630 after dosing on the intermittent schedule is shown in Table 4 and Figure 9a.

The median half-life of RMC-4630 was approximately 28 and 33 hours following a single dose at 140 and 200 mg, respectively. No accumulation from day 1 to day 15 was observed with either D1,D4 dosing or D1,D2 dosing schedules. Plasma exposure at all dose levels was within the range anticipated to be biologically active from preclinical models. At 200 mg D1,D2, the C_{max} concentrations were generally above those thought to represent the 'apoptotic threshold' or plasma concentration at which RMC-4630 can best induce tumor cell death (Figure 9a). In addition, trough concentrations towards the end of the week were below those thought to be required for normal tissue recovery. This is consistent with the improved safety/tolerability of the D1,D2 schedule. The pharmacokinetic profile of the 200 mg D1,D2 schedule seems to represent the one closest to that associated with an optimal therapeutic index in preclinical models, compared with the maximum tolerated dose at the alternative schedules (60 mg daily or 140 mg D1,D4).

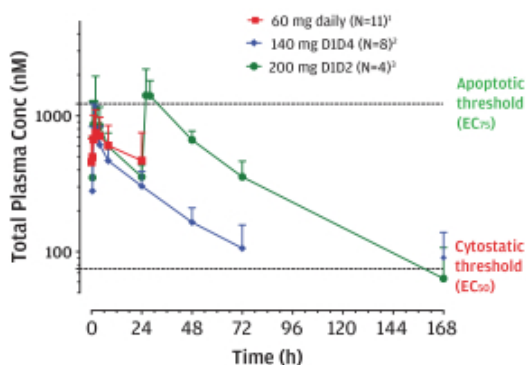
Table 4: Pharmacokinetics—intermittent schedule in RMC-4630-01 study.

Study	Schedule	Dose	Cycle/Day	N(C _{max} /AUC)	PK parameters [Mean(CV%)]					
					C _{max}	Median T _{max} (range)	AUC ₀₋₂₄	Mean accumulation (AUC ₀₋₂₄ ratio)	AUC ₀₋₇₂	Median t _{1/2} (range)
					µM	h	µM*h		µM*h	H
Mouse efficacy	QD steady state	10 mg/kg			0.98		6.44		NA	NA
		20 mg/kg			3.4		11.7			
RMC-4630-01	Twice weekly (D1, D4)	140 mg	1/1	8/8	0.915 (50)	2 (1-8)	10.8 (35)		19.7 (31)	28 (23-33)
			1/15	8/8	0.935 (35)	2 (2-4)	14.0 (41)	1.3	NA	NA
		200 mg	1/1	18/18	1.38 (41)	2 (0.5-8)	17.5 (38)		39.0 (40)	33 (20-40)
			1/15	12/12	1.23 (32)	3 (1-24)	18.6 (31)	1.1	NA	NA
	Twice weekly (D1, D2)	200 mg	1/1	4/4	1.58 (45)	3 (2-4)*	13.9 (33)		NA	NA
			1/15	3/3	1.63 (25)	2 (2-2)	14.5 (18)	1.0	NA	NA

* T_{max} value was time post D2 or D16 dosing for 200 mg (D1, D2)

Data as of May 4, 2020.

Figure 9a: Plasma Concentration over Time Profiles



PK sampled at:

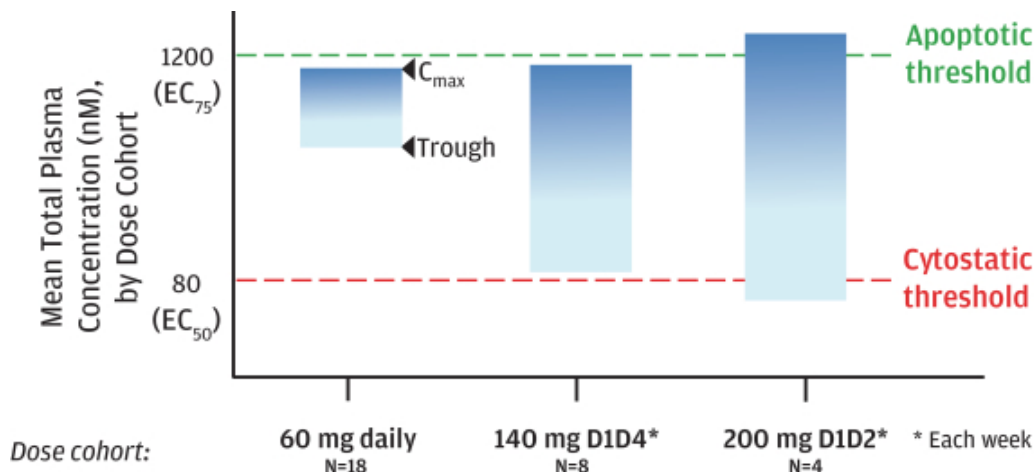
¹C1D22

²Post-C1D1 dosing and C1D8 trough (~168 h)

³Post-C1D1 and C1D2 dosing and C1D8 trough (~168 h)

RMC-4630 was dosed daily at 60 mg or intermittent twice weekly at 140 mg (D1, D4) or 200 mg (D1, D2). For 60 mg daily dosing, plasma concentration profile was from Cycle 1 Day 22 (steady state). For 140 mg (D1, D4) and 200 mg (D1, D2) schedules, plasma concentration profiles from week 1 were presented. No accumulation was observed following twice weekly dosing. The dotted lines on the plot indicate the cytostatic and apoptotic thresholds and represent the approximate plasma concentrations required to inhibit RAS pathway activity in tumor xenograft models in mice *in vivo* by 50% (EC₅₀) and 75% (EC₇₅) respectively. These thresholds are based on the preclinical anti-tumor activity of RMC-4630 *in vivo* in the NCI-H358 KRAS^{G12C} xenograft model. Lower doses of RMC-4630 (10 mg/kg daily) produced durable coverage (12-16 hr) over the EC₅₀ but did not exceed the EC₇₅ and were associated with tumor growth inhibition (cytostatic threshold) but not regressions. Tumor regressions (apoptotic threshold) were observed for higher doses (30 mg/kg daily) at which the plasma exposures exceeded the EC₇₅ for 4-6 hr and the EC₅₀ for the entire dosing interval. A single dose of 30 mg/kg of RMC-4630 has been shown to induce apoptosis *in vivo* in the KRAS^{G12C} pancreatic tumor cell line MIA PaCa-2. The actual plasma concentration at which cell death (apoptosis) may occur may vary from tumor to tumor. It should be noted also that in *in vitro* studies the induction of apoptosis in KRAS^{G12C} tumor cell lines is both concentration and time-dependent. Characterization of RAS pathway activation has not been performed for normal tissue. However, in *in vivo* rodent studies, lower trough plasma concentrations (below EC₅₀) have been associated with improved tolerability.

Figure 9b: Schematic representation of RMC-4630 pharmacokinetics at three tolerated dose schedules with peak and trough concentrations of RMC-4630 derived from the data from Figure 9a and Table 4.



Schematic depiction of the pharmacokinetic profiles in humans of three tolerated dosing regimens; daily at 60 mg, intermittent twice weekly at 140 mg (D1, D4) and intermittent twice weekly at 200 mg (D1, D2). Blue bars indicate the C_{max} and Trough plasma concentrations for the respective dose regimens (see also Table 4 and Figure 9a). Pharmacokinetic profiles for the 60 mg daily group were available from N=11. The cytostatic and apoptotic thresholds are defined in the legend to Figure 9a.

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Forty-nine patients have been treated in RMC-4630-01 with the daily schedule. Median RMC-4630 exposure is 1.8 months (range 0.0-16.3 months). Demographic and baseline characteristics information is shown in Table 5.

Table 5: Demographics and baseline characteristics—daily schedule in RMC-4630-01 study.

	20 mg (N=12)	40 mg (N=13)	60 mg (N=18)	80 mg (N=6)
Age, median (range)	62.5 (34-76)	65.0 (45- 84)	60.5 (47-82)	62.0 (40-75)
Male	9 (75.0%)	8 (61.5%)	9 (50.0%)	1 (16.7%)
Cancer Type				
Lung	6 (50.0%)	4 (30.8%)	10 (55.6%)	1 (16.7%)
Colon and/or Rectal	3 (25.0%)	5 (38.5%)	5 (27.8%)	3 (50.0%)
Other	3 (25.0%)	4 (30.8%)	3 (16.7%)	2 (33.3%)
ECOG performance status				
0	6 (50.0%)	3 (23.1%)	6 (33.3%)	3 (50.0%)
1	6 (50.0%)	10 (76.9%)	12 (66.7%)	3 (50.0%)
Number of prior cancer therapies, median (range)	3.0 (1-11)	4.0 (2-11)	5.0 (1-11)	4.5 (2-8)

Data as of May 4, 2020.

The ECOG (Eastern Cooperative Oncology Group) performance status is a scale often used to describe patients' level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.).

Although both dosing regimens have been reasonably well tolerated, daily dosing has been associated with more frequent and severe AEs than the intermittent schedule. As with the intermittent schedule, the safety profile from the daily dosing schedule has been consistent with the mechanistic effects of the product candidate on SHP2 and the RAS signaling pathways. We have not determined a maximum tolerated dose for daily dosing, although dose escalation will not continue beyond the 80 mg daily level already evaluated. If further development with this schedule was pursued, we expect the recommended Phase 2 dose for the daily schedule would be 60 mg daily.

Treatment-related AEs occurring in greater than or equal to 10% of patients who received the daily schedule are shown in Table 6. No toxicities consistent with 'off-target' effects have been reported. Increases in liver enzymes such as alanine transaminase and aspartate transaminase have been observed at all grades. These have been attributed, wholly or in part, to RMC-4630 in 10.2% or 18.4% of patients treated with the daily schedule, respectively. In two patients, the increase in alanine transaminase or aspartate transaminase was either grade 3 or grade 4.

Table 6: Related AEs occurring in ³ 10% of dosed patients by grade – daily schedule in RMC-4630-01 study.

Preferred Term	Overall (N=49)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Thrombocytopenias (SMQ)*	15 (30.6%)	4 (8.2%)	3 (6.1%)	6 (12.2%)	2 (4.1%)
Diarrhea	13 (26.5%)	8 (16.3%)	4 (8.2%)	1 (2.0%)	—
Anemias (SMQ)**	12 (24.5%)	1 (2.0%)	5 (10.2%)	6 (12.2%)	—
Aspartate aminotransferase increased	9 (18.4%)	5 (10.2%)	2 (4.1%)	1 (2.0%)	1 (2.0%)
RevMed Edemas (CMQ)***	9 (18.4%)	6 (12.2%)	1 (2.0%)	2 (4.1%)	—
Fatigue	8 (16.3%)	3 (6.1%)	5 (10.2%)	—	—
Hypertension	7 (14.3%)	—	3 (6.1%)	4 (8.2%)	—
Dry mouth	6 (12.2%)	6 (12.2%)	—	—	—
Nausea	6 (12.2%)	6 (12.2%)	—	—	—
Alanine aminotransferase increased	5 (10.2%)	3 (6.1%)	—	2 (4.1%)	—

Data as of May 4, 2020. Abbreviations: SMQ, Standardized MedDRA Query; CMQ, Customized MedDRA Query.

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* Includes platelet count decrease.

** Includes hemoglobin decrease.

*** Consists of eyelid edema, face edema, generalized edema, lip edema, edema, edema peripheral, periorbital edema and peripheral swelling.

Eight patients treated with the daily schedule have experienced toxicities involving the lungs or respiratory system that were attributed in part to RMC-4630 by the treating investigator. These were generally moderate or mild. One additional case of grade 4 respiratory failure is discussed in more detail below in the description of SAEs. No data has been reported suggesting that systemic activation of the immune system is associated with toxicity in subjects treated with RMC-4630 monotherapy. There have been no reports of pneumonitis. Related adverse events involving other important organs such as the heart, brain and kidneys have been uncommon and generally mild to moderate in severity.

Three patients (6%) had SAEs thought to be possibly or probably related to the study drug as assessed by the trial sponsor. One Grade 2 event of dehydration was reported in the 60 mg daily cohort. One Grade 4 event of thrombocytopenia and one Grade 3 event of generalized edema were reported in the 80 mg daily cohort. Two additional SAEs, both in the 60 mg daily cohort, were reported in which the investigator was unable to rule out an association with the study drug, but where the evidence for causality by RMC-4630 was absent or considered unlikely by the study sponsor. One patient with extensive metastases of tumor in the lungs developed Grade 4 respiratory failure and was hospitalized and treated with oxygen. The SAE was ongoing when the patient was withdrawn from the study. The SAE was ongoing when the patient died due to progression of underlying cancer. A second patient developed a single reading of Grade 3 prolongation of QTc. This patient had been receiving 60 mg daily of RMC-4630 but had not received any dose for three days at the time of the reading. The patient had a previous history of prolonged QTc, underlying systemic lupus, and was taking ondansetron. QTc was prolonged (grade 1) at baseline. Five hours after the prolonged QTc reading, the patient had two follow-up ECGs that showed normal QTc interval.

Table 7: Early data suggest intermittent schedule may be better tolerated than daily schedule in RMC-4630-01 study.

Related adverse events occurring in ³ 10% of patients	Related AEs Daily (N=49)		Related AEs Intermittent (N=38)	
	Any grade	Grade ³ 3	Any grade	Grade ³ 3
Thrombocytopenias (SMQ)*	15 (30.6%)	8 (16.3%)	10 (26.3%)	2 (5.3%)
Diarrhea	13 (26.5%)	1 (2.0%)	15 (39.5%)	2 (5.3%)
Anemias (SMQ)**	12 (24.5%)	6 (12.2%)	10 (26.3%)	4 (10.5%)
Aspartate aminotransferase increased	9 (18.4%)	7 (14.3%)	3 (7.9%)	0
RevMed Edemas (CMQ)***	9 (18.4%)	2 (4.1%)	8 (21.1%)	0
Fatigue	8 (16.3%)	0	10 (26.3%)	1 (2.6%)
Hypertension	7 (14.3%)	4 (8.2%)	1 (2.6%)	0
Dry mouth	6 (12.2%)	0	2 (5.3%)	0
Nausea	6 (12.2%)	0	7 (18.4%)	2 (5.3%)
Alanine aminotransferase increased	5 (10.2%)	2 (4.1%)	3 (7.9%)	0
Vomiting	3 (6.1%)	0	6 (15.8%)	2 (5.3%)

Data as of May 4, 2020. Abbreviations: SMQ, Standardized MedDRA Query; CMQ, Customized MedDRA Query

* Includes platelet count decrease.

** Includes hemoglobin decrease.

*** Consists of eyelid edema, face edema, generalized edema, lip edema, edema, edema peripheral periorbital edema, and peripheral swelling.

Pharmacokinetics—daily dosing schedule

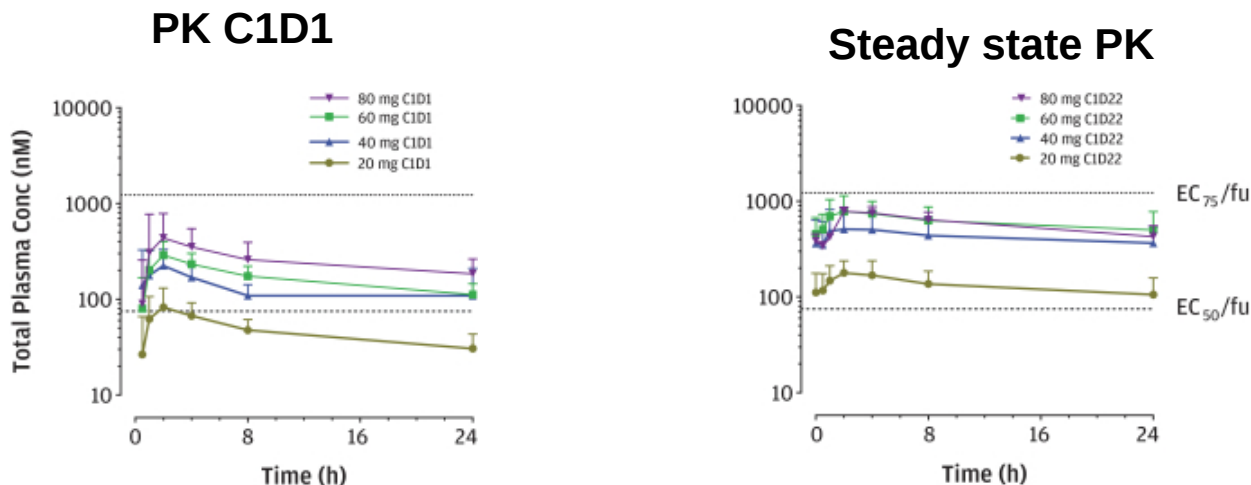
With daily dosing, plasma concentrations of RMC-4630 reached a steady state by day 22 (Table 8 and Figure 10). Plasma concentrations of RMC-4630 in the blood at all daily dose levels were consistently higher than the *in vivo* EC₅₀ for pERK in tumor models. Exposure increased approximately proportionally with increasing dose. The total exposure to RMC-4630 over a 24-hour period at 60 mg daily was 14.6 uM.hr. This is more than twice the exposure that has been required to see anti-tumor effects, particularly tumor stasis, in animal models (6.44 uM.hr).

Table 8: Pharmacokinetics—daily schedule in RMC-4630-01 study.

Study	Schedule	Dose	Cycle	Day	N(Cmax/AUC)	PK parameters [Mean(CV%)]				AUC 0-72 μM*h	Median t _{1/2} (range) h
						C _{max}	Median T _{max} (range) h	AUC 0-24	Mean accumulation (AUC Ratio)		
						μM		μM*h			
Mouse efficacy		10 mg/kg				0.98		6.44			
		30 mg/kg				4.81		22.8			
RMC-4630-01	QD	20 mg	1	1	12/11	0.0852 (54)	2 (1-4.6)	1.06 (40)	3.0	NA	NA
			1	22	11/9	0.191 (36)	2 (1-4)	3.19 (37)			
		40 mg	1	1	13/13	0.267(58)	2 (0.5-24)	3.14(48)			
			1	22	9/9	0.556 (54)	4 (1-8)	10.3 (53)			
		60 mg	1	1	16/16	0.318 (29)	2 (0.5-8)	3.97 (24)			
			1	22	9/9	0.857 (45)	2 (1-8)	14.6 (44)			
		80 mg	1	1	6/6	0.472 (84)	3 (1-4)	6.03 (56)			
			1	22	2/2	0.844	3 (2-4)	13.9			

Data as of October 8, 2019. Number of patients evaluated for parameters C_{max} and AUC are shown in N(C_{max}/AUC) column.

Figure 10: Pharmacokinetics—daily schedule in RMC-4630-01 study.



Data as of October 8, 2019.

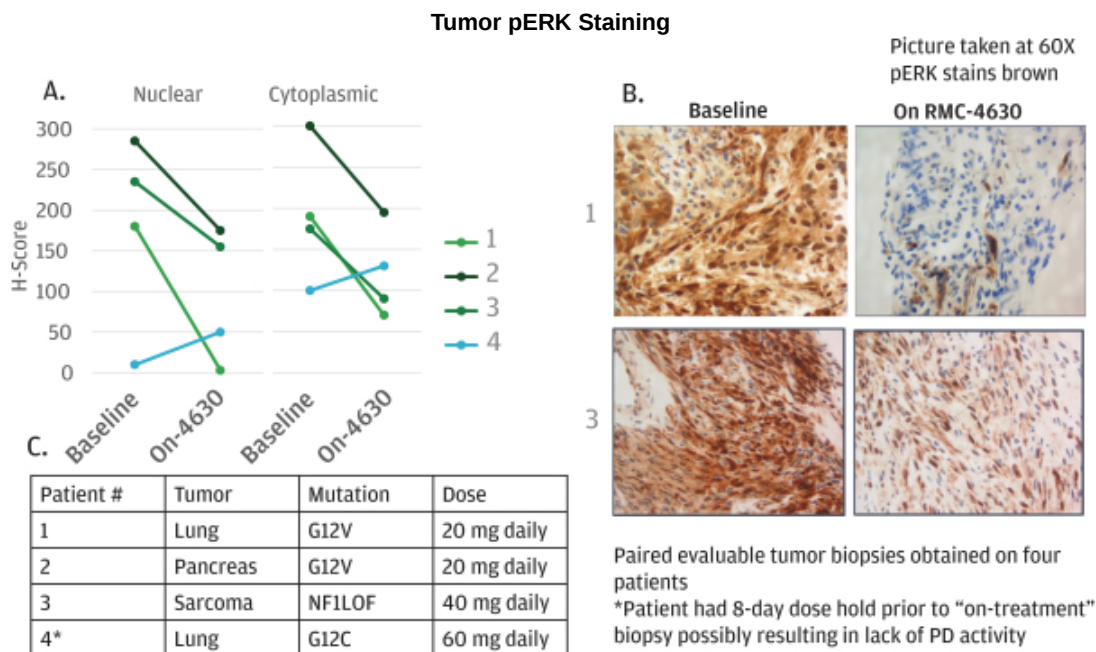
Pharmacokinetic profile of RMC-4630 dosed at either 20 mg, 40 mg, 60 mg or 80 mg daily. Steady state is considered to be day 22 of cycle 1. EC₅₀/fu and EC₇₅/fu are the total estimated plasma concentrations in humans that correspond to 50% and 75% inhibition of pERK in KRAS^{G12C} tumor models.

Pharmacodynamic effects of RMC-4630—daily and intermittent dosing schedules

Activation of the protein ERK, which is an important protein in the RAS signaling pathway and a substrate for MEK, is a good surrogate for the inhibition of pathway activity by a SHP2 inhibitor. The pharmacodynamic effects of RMC-4630 on activation of ERK were studied in the blood cells of patients being treated with RMC-4630. Despite considerable assay variability and inter-patient variability, which is common for these types of dynamic assays in patients, there was a trend in favor of inhibition of activated ERK in peripheral blood cells at all dose levels tested. These effects are consistent with engagement and inhibition of the SHP2 target and downstream RAS signaling by RMC-4630.

Phosphorylation of ERK has been assessed in tumors before and during RMC-4630 administration (Figure 11). In three cases, there was a reduction in phosphorylation of cytoplasmic and nuclear ERK in the tumor while RMC-4630 was at steady state. One patient's tumor showed no reduction in tumor pERK, but this tumor showed very little phosphorylation in the pre-treatment sample and the patient had not received any RMC-4630 for eight days prior to the second tumor biopsy.

Figure 11: pERK inhibition in tumors on RMC-4630 in RMC-4630-01 study.



Quantitation of phospho-ERK (pERK) in tumor tissue taken from patients treated with daily RMC-4630 at either 20 mg, 40 mg or 60 mg daily. Panel A represents the H score for pERK before and after dosing in four patients. H score is the product of percentage of tumor cells staining positive for pERK and the intensity of staining per cell. Both nuclear and cytoplasmic pERK are shown. Panel B shows the immunohistochemistry sections from which the H score is estimated. pERK stains brown. Panel C provides information for each patient on whom paired biopsies were obtained.

Allelic burden of circulating KRAS^{G12C} tumor DNA, or ctDNA, has been assessed prior to the study and at least once during the study in seven patients with tumors harboring KRAS^{G12C}. KRAS^{G12C} ctDNA was detected in four of seven patients prior to the study. In two patients, with NSCLC and either partial response or stable disease as best response, there was a reduction in circulating KRAS^{G12C} ctDNA. In one patient with colon cancer who had a progressive disease the allelic frequency of KRAS^{G12C} ctDNA increased.

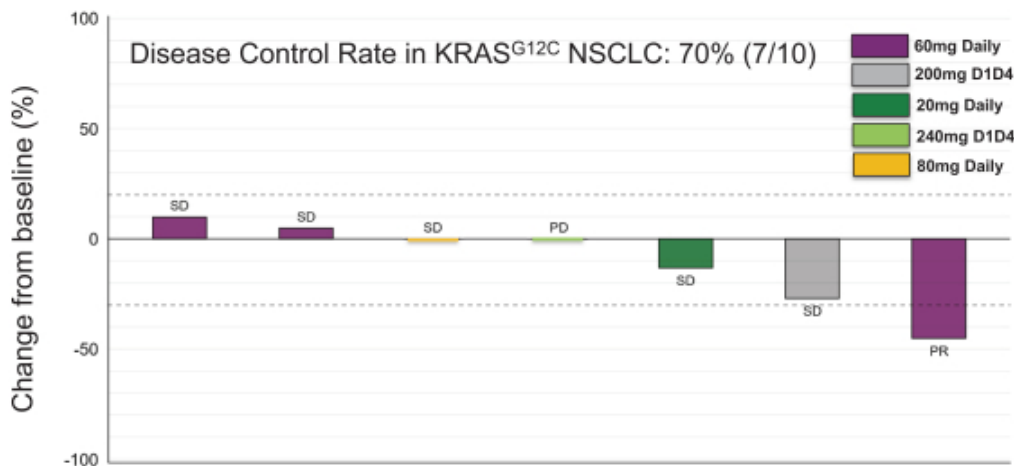
Interim evidence of clinical activity—daily and intermittent schedules

There is preliminary evidence that RMC-4630 has single agent anti-tumor activity in KRAS mutant NSCLC and in NF1^{LOF} tumors. As of the data extract of May 4, 2020, seven patients with KRAS^{G12C} NSCLC had follow-up CT scans of target lesions. Among them, one had partial response, five had stable disease, and one had disease progression (Figure 12); three patients had not reported follow-up measurements of target lesions, of which one has been recorded as best response of stable disease and two of progressive disease. Disease control rate, or DCR, the sum of best response of partial response and stable disease cases for patients with KRAS^{G12C} NSCLC as of the extract date was 7/10 (70%).

For all patients with KRAS mutant NSCLC, DCR was 17/29 (59%) (Figure 13). One patient with KRAS^{G12V} NSCLC was on treatment for 16.3 months with stable disease (and approximately 15% reduction in tumor volume) as of the cut-off date. Duration of treatment, time to first and best response, duration of response and time to progression in NSCLC patients with any KRAS mutation are shown in Figure 14.

In histotypes other than NSCLC, the best response for tumors harboring a KRAS mutation, as of the cut-off date, was stable disease.

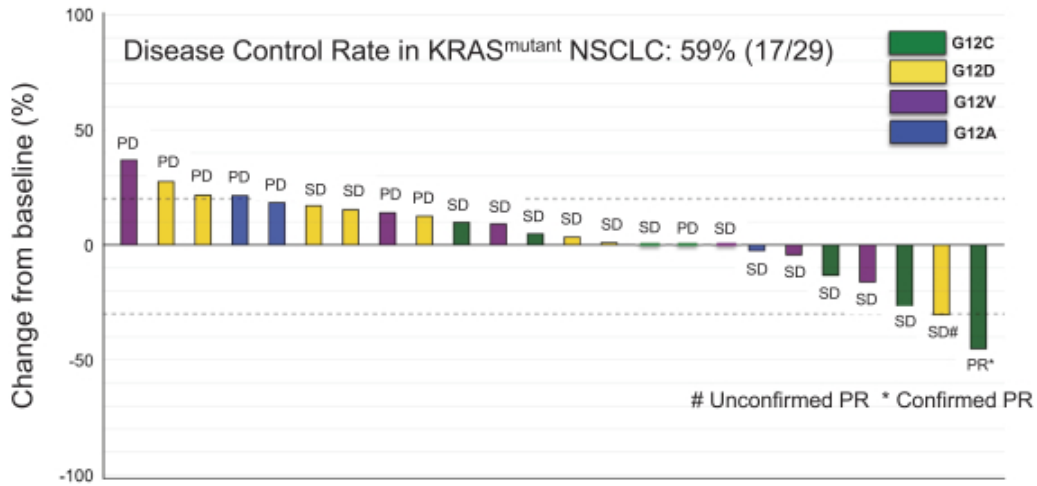
Figure 12: Best change in tumor burden from baseline in KRAS^{G12C} NSCLC in RMC-4630-01 study.



Data as of May 4, 2020.

Waterfall plot of best tumor response for five patients with KRAS^{G12C} NSCLC who had baseline target lesions assessed and at least one radiologic follow-up assessment of target lesion size. Percentage (Y axis) represents the percentage change from baseline in the Sum of Longest Diameters of target lesions using RECIST 1.1. Colors represent different dose levels. Data are presented for the efficacy evaluable population (N=10) defined as participants with baseline and at least one post-baseline scan or who died or had clinical progression prior to first post-baseline scan. Three patients are not represented in this figure: 2 PD (1 death due to clinical progression prior to first scan and 1 did not have measurement for one of the target lesions but had new lesion) and 1 SD (had partial missing tumor measurements in the database at the time of data extract).

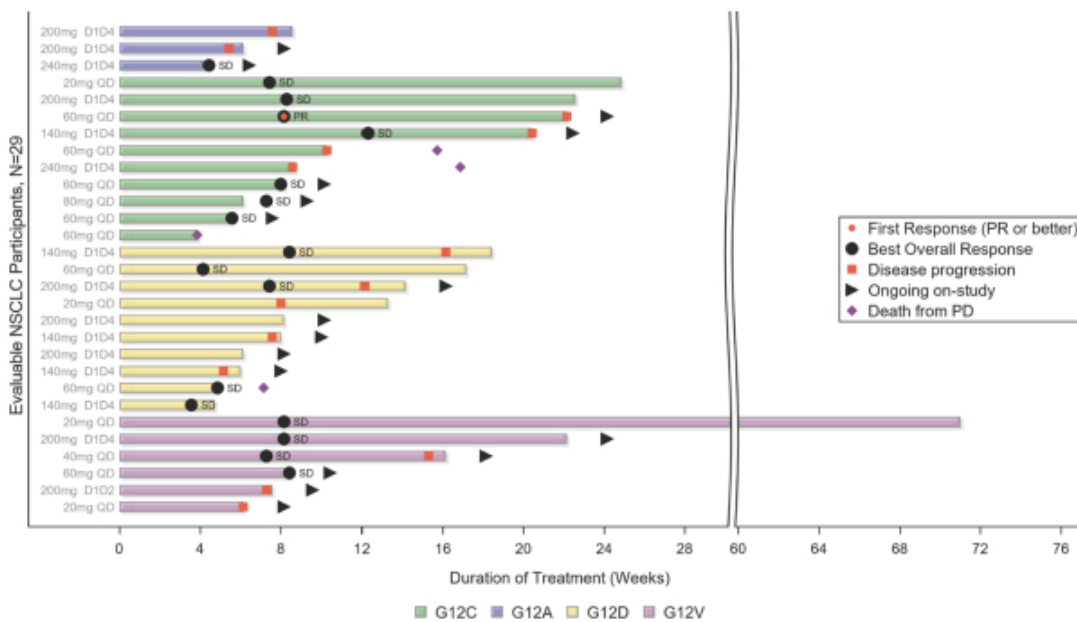
Figure 13: Best change in tumor burden from baseline for NSCLC with any KRAS mutation in RMC-4630-01 study.



Data as of May 4, 2020.

Waterfall plot of best tumor response for fourteen patients with KRAS mutant NSCLC, including KRAS^{G12C}, who had baseline target lesions assessed and at least one radiologic follow-up assessment of target lesion size. Percentage (Y axis) represents the percentage change from baseline in the Sum of Longest Diameters of target lesions using RECIST 1.1. Colors represent different KRAS mutations. Data are presented for the efficacy evaluable population (N=29) defined as participants with baseline and at least one post-baseline scan or who died or had clinical progression prior to first post-baseline scan. Five patients are not represented in this figure: 1 patients had death due to clinical progression prior to first scan, 1 patient did not have measurements for one of the target lesions but progressed developing new lesion, and 3 patients had missing tumor measurements in the database at the time of data extract.

Figure 14: Duration of treatment, time to and duration of response in NSCLC with any KRAS mutation in RMC-4630-01 study.



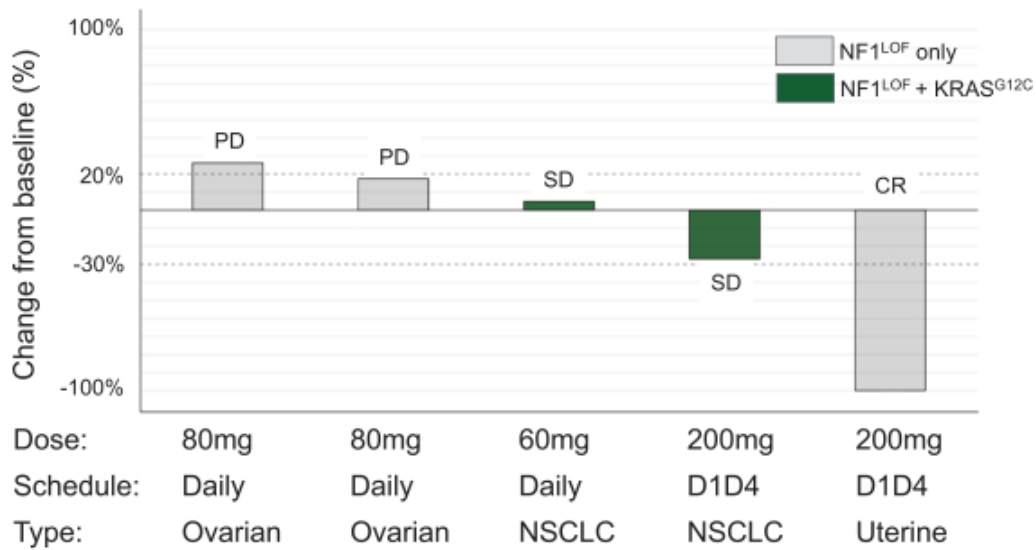
Data as of May 4, 2020.

Swimmer plot of duration of treatment, time to first and best response, duration of response and time to progression for eighteen patients with KRAS mutant NSCLC, including KRAS^{G12C}. Percentage (Y axis) represents each individual patient. Colors represent different KRAS mutations. Data are presented for the efficacy evaluable population (N=29) defined as participants with baseline and at least one post-baseline scan or who died or had clinical progression prior to first post-baseline scan.

Single agent activity of RMC-4630 has also been reported in two patients with tumors harboring NF1^{LOF} mutations. One patient, a 63 year old female with a poorly differentiated uterine carcinosarcoma, had a complete response. This patient was diagnosed in October 2017 with a tumor harboring two NF1^{LOF} mutations, a POLE (DNA repair) mutation, and ultra-high tumor mutational burden. The patient had received two treatment regimens prior to starting RMC-4630. She started RMC-4630 200 mg D1D4 and was subsequently reduced to 140 mg D1D4 due to gastrointestinal toxicity. At two months, her tumor dimension had reduced from 1.7 cm to undetectable. CR was subsequently confirmed and she continues in CR at five months on study therapy.

A second patient with NSCLC harboring a co-existing NF1^{LOF} and KRAS^{G12C} had tumor shrinkage (Figure 15a).

Figure 15a: Waterfall plot of patients with NSCLC or gynecologic tumors harboring NF1^{LOF} treated with RMC-4630.



Data as of May 4, 2020.

Data are presented for the efficacy evaluable population (N=6) defined as participants with baseline and at least one post-baseline scan or who died or had clinical progression prior to first post-baseline scan. One patient (NSCLC) with death due to clinical PD prior to first scan is not represented in this figure. NF1^{LOF} is loss, or significant reduction, in neurofibromin protein function is presumed from nature of mutation.

RMC-4630-02 study of RMC-4630 in combination with cobimetinib in patients with advanced solid tumors

RMC-4630-02 is a Phase 1b/2 study of RMC-4630 in combination with the MEK inhibitor cobimetinib in patients with advanced cancers that harbor mutations in the RAS signaling pathway. The study is designed to evaluate the safety, tolerability and pharmacokinetics of RMC-4630 and cobimetinib under two different dose administration schedules.

The objective of this study is to determine a recommended dose and schedule and further test clinical activity of the combination. Initially, the study assesses twice weekly RMC-4630 with daily (21 days on, 7 off) cobimetinib. A preliminary evaluation of anti-tumor activity is also being made. Alternative dosing schedules using intermittent dosing of one or both RMC-4630 and cobimetinib are also under evaluation.

Data are provided here for eight patients that had been enrolled, had received study medication at the first dose level and were evaluable for safety as of November 14, 2019. Enrollment has continued in additional dose cohorts in this ongoing study.

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Interim safety and tolerability

Eight patients have been evaluated for safety with a median RMC-4630 exposure of 1.4 months (range 0.1 – 2.5 months). Demographic and baseline characteristics information is shown in Table 9.

Table 9: Demographics and baseline characteristics for RMC-4630-02 study.

	RMC-4630 80 mg D1,D4 Cobimetinib 20 mg QD 21/7 (N=8)
Age, median (range)	61.5 (35.0 – 64.0)
Male (%)	3 (37.5%)
Cancer Type	
Lung (%)	—
Colon and/or Rectal (%)	5 (62.5%)
Pancreatic (%)	2 (25.0%)
Ovarian (%)	1 (12.5%)
ECOG performance status	
0	5 (62.5%)
1	3 (37.5%)
Number of prior cancer therapies, median (range)	4 (2 – 6)

Data as of November 14, 2019.

The ECOG (Eastern Cooperative Oncology Group) performance status is a scale often used to describe patients' level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.).

The emerging safety profile is consistent with the mechanistic effects of both SHP2 inhibition and MEK inhibition, including edema, diarrhea and other gastrointestinal toxicity, anemia and rash. This safety profile was largely predictable from single agent clinical studies of both agents.

Table 10: Related AEs attributed to RMC-4630 in RMC-4630-02 study.

Preferred term	Any grade	Grade 1	Grade 2	Grade 3
Diarrhea	2 (25.0%)	2 (25.0%)	—	—
Edema*	2 (25.0%)	1 (12.5%)	1 (12.5%)	—
Abdominal discomfort	1 (12.5%)	1 (12.5%)	—	—
Abdominal distension	1 (12.5%)	—	1 (12.5%)	—
Blood creatinine increased	1 (12.5%)	1 (12.5%)	—	—
Dry mouth	1 (12.5%)	1 (12.5%)	—	—
Leukopenia	1 (12.5%)	1 (12.5%)	—	—
Nephropathy	1 (12.5%)	1 (12.5%)	—	—
Rash	1 (12.5%)	—	—	1 (12.5%)
Rash maculo-papular	1 (12.5%)	1 (12.5%)	—	—

Data as of November 14, 2019.

* Consists of eyelid edema, face edema, generalized edema, lip edema, edema, edema peripheral, periorbital edema and peripheral swelling.

Table 11: Related AEs attributed to cobimetinib in RMC-4630-02 study.

Preferred term	Any grade	Grade 1	Grade 2	Grade 3
Edema*	2 (25.0%)	1 (12.5%)	1 (12.5%)	—
Abdominal discomfort	1 (12.5%)	1 (12.5%)	—	—
Abdominal distension	1 (12.5%)	—	1 (12.5%)	—
Blood creatinine increased	1 (12.5%)	1 (12.5%)	—	—
Decreased appetite	1 (12.5%)	1 (12.5%)	—	—
Dizziness	1 (12.5%)	1 (12.5%)	—	—
Diarrhea	1 (12.5%)	1 (12.5%)	—	—
Leukopenia	1 (12.5%)	1 (12.5%)	—	—
Rash	1 (12.5%)	—	—	1 (12.5%)
Rash maculo-papular	1 (12.5%)	1 (12.5%)	—	—

Data as of November 14, 2019.

* Consists of eyelid edema, face edema, generalized edema, lip edema, edema, edema peripheral, periorbital edema and peripheral swelling.

Pharmacokinetics

The pharmacokinetic profiles of RMC-4630 and cobimetinib are shown in Table 13 and Figure 15b. Plasma levels of RMC-4630 were consistent with those obtained in the RMC-4630-01 study and were continuously greater than our predicted EC₅₀ for pERK inhibition in preclinical tumor models.

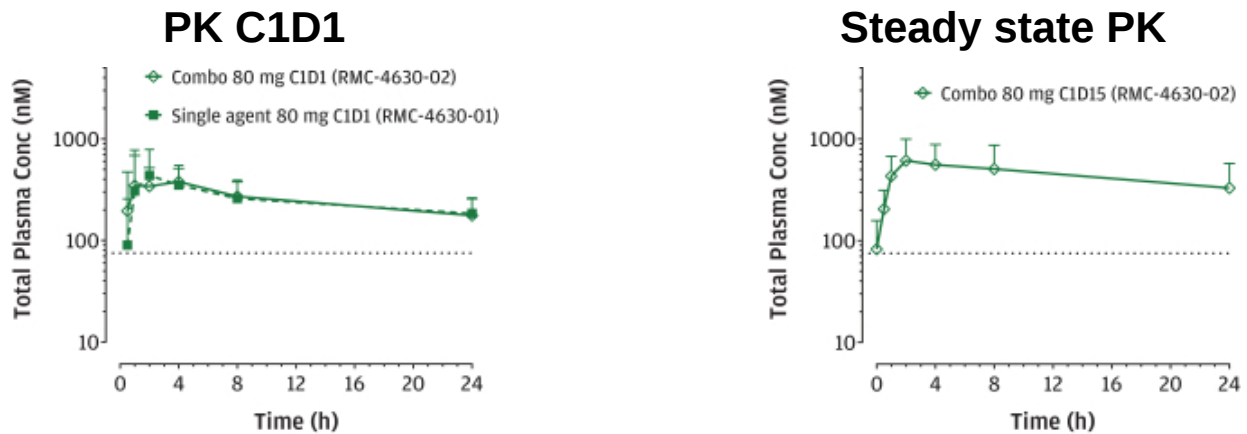
Table 12: Summary of pharmacokinetics in the RMC-4630-02 study.

Study	Dose (mg)		Analyte	Cycle	Day	N(Cmax/AUC)	PK parameters [Mean(CV%)]			
	RMC-4630	Cobimetinib					C _{max} (μM)	Median T _{max} (range) (h)	AUC ₀₋₂₄ (μM*h)	Mean accumulation (AUC Ratio)
RMC-4630-02	80	20	RMC-4630	1	1	8/8	0.518 (47)	3 (1-4)	6.14 (35)	1.7
					15	5/5	0.657 (53)	2 (1-4)	10.7 (67)	
	15	1	Cobimetinib	1	8/8	0.126 (71)	2 (1-4)	1.55 (85)		
				15	5/5	0.374 (41)	2.2 (1-8)	7.09 (51)		
RMC-4630-01	80	NA	RMC-4630	1	1	6/6	0.472 (84)	3 (1-4)	6.03 (56)	4.6
					22	2/2	0.844	3 (2-4)	13.9	

Data as of November 1, 2019.

Number of patients evaluated for parameters C_{max} and AUC are shown in N(C_{max}/AUC) column.

Figure 15b RMC-4630 pharmacokinetics in RMC-4630-02 study.



Data as of November 1, 2019.

Clinical activity

Only two patients have been evaluated for efficacy in this study. No efficacy data or ctDNA data were available in the electronic database as of the cut-off date.

Ongoing and planned clinical studies with RMC-4630

The RMC-4630-01 Phase 1 study is continuing to enroll patients to determine the maximum tolerated dose and recommended Phase 2 dose for the intermittent dosing schedule. Alternative intermittent schedules are being explored as part of the RMC-4630-01 study and these data may be translated to ongoing combination studies or future studies.

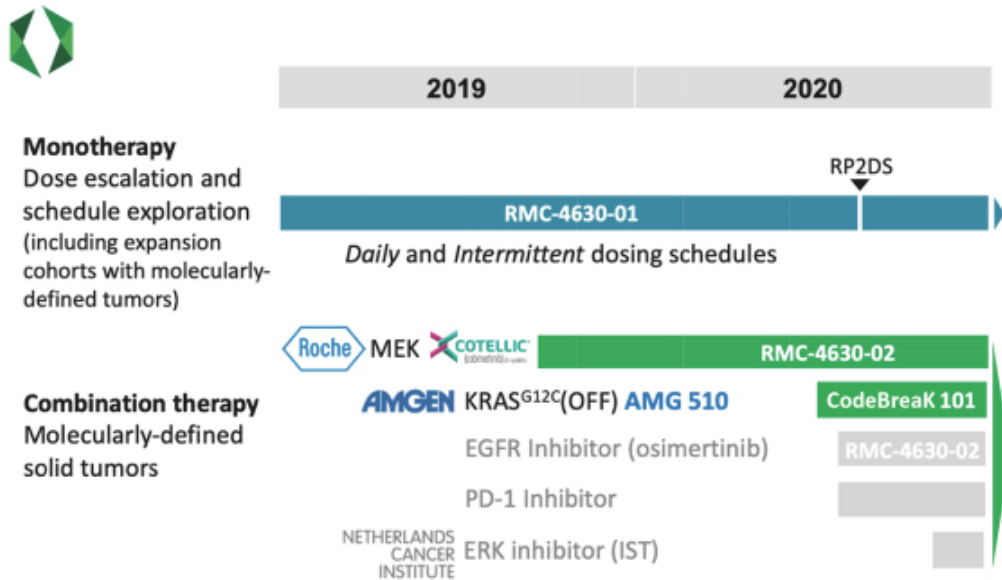
The RMC-4630-02 study, evaluating intermittent dosing of RMC-4630 in combination with cobimetinib, has been activated and dose escalation is ongoing.

An arm in Amgen’s CodeBreak 101 study, evaluating RMC-4630 in combination with its investigational agent sotorasib, was recently initiated by Amgen.

In collaboration with others, during 2020, we intend to start dosing patients in Phase 1b studies evaluating the combination of RMC-4630 with the EGFR inhibitor osimertinib, and with a PD-1 inhibitor (Figure 16). Sanofi, our SHP2 collaboration partner, plans to sponsor the RMC-4630 with PD-1 inhibitor combination study.

In March 2020, the Pancreatic Cancer Collective (a strategic partnership between Lustgarten Foundation and Stand Up To Cancer) announced that it had awarded funding to the Netherlands Cancer Institute, or the NKI, for its study using our SHP2 inhibitor, RMC-4630 in combination with an investigational ERK inhibitor in patients with pancreatic cancer. We plan to provide RMC-4630 to support this investigator sponsored study.

Figure 16: Phase 1/2 planned clinical development program for RMC-4630.



Our RAS(ON) portfolio

Overview

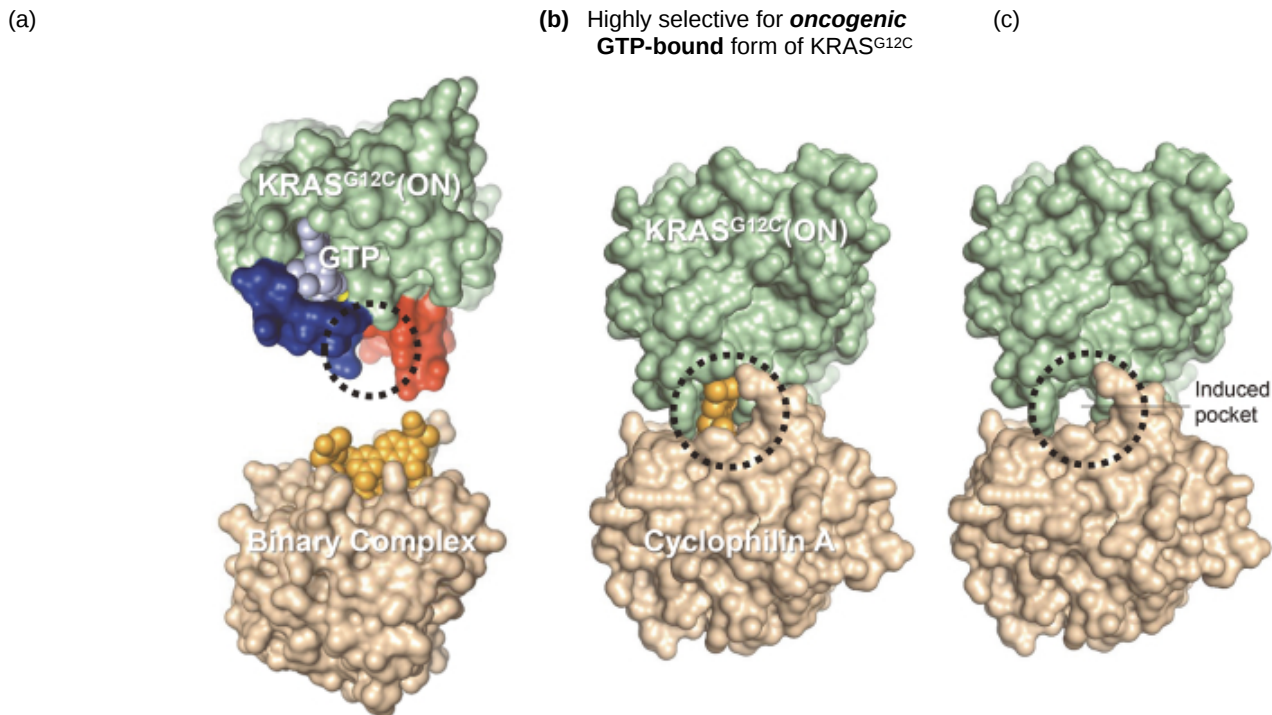
We are also developing a portfolio of what we believe to be the first potent, selective and cell-active inhibitors of mutant RAS(ON) proteins. These inhibitors have also exhibited anti-tumor activity *in vivo* in preclinical models. We believe that direct inhibitors of RAS(ON) will suppress cell growth and survival as well as be less susceptible to adaptive resistance mechanisms recognized for RAS(OFF) inhibitors. Initially, we will prioritize four mutant RAS(ON) targets—KRAS^{G12C}, KRAS^{G13C}, KRAS^{G12D} and NRAS^{G12C}—and expect to nominate our first development candidate in 2020. We plan to evaluate our RAS(ON) inhibitors alone and in combination with other drugs and investigational new drugs, particularly in-pathway agents. Our proprietary tri-complex technology platform provides us the opportunity to build a portfolio of genetically targeted RAS(ON) inhibitors by discovering and developing compounds that target diverse oncogenic RAS mutants.

Challenges and limitations of current approaches for RAS mutant cancers

To our knowledge, every targeted therapy approved or in clinical development for the treatment of RAS-dependent cancers acts on targets that lie either upstream or downstream of RAS(ON) within the cellular signaling cascade. Historically, direct inhibition of any RAS protein has been challenging due to a lack of tractable, or “druggable,” binding pockets. However, selective inhibitors of the inactive GDP-bound, or “OFF” form, of KRAS^{G12C} are being developed by several companies. Recently reported initial clinical results from two RAS(OFF) inhibitors targeting mutant KRAS^{G12C} suggest significant clinical benefit and provide strong pharmacologic validation of this oncoprotein as a cancer driver. These results, along with other preclinical data, provide a compelling basis for our commitment to targeting oncogenic mutant forms of RAS(ON). We are not aware of any programs in clinical development that have successfully targeted any RAS(ON) protein. In tumor cells addicted to RAS(ON), we believe that selective inhibitors of RAS(ON) will suppress cell growth and survival and be less susceptible to adaptive resistance mechanisms recognized for RAS(OFF) inhibitors.

The key drug discovery challenge for any known RAS(ON) protein is the absence of a tractable drug binding site on these RAS(ON) proteins, including different RAS isoforms and mutants. One molecular site of particular focus has been a switch region protein shallow, solvent-exposed groove, or “valley,” that has been detected exclusively in the GTP-bound forms of RAS. Our proprietary tri-complex technology enables us to discover small molecule compounds that inhibit this site by inducing new druggable pockets. This approach is inspired by a biological phenomenon observed in nature, as exemplified by rapamycin. These tri-complexes exploit the surfaces of the two adjacent proteins to form a new ligand-binding pocket. The chaperone protein in the tri-complex helps to form the ligand binding site for the small molecule compound. Further, by physically participating in the tri-complex in the presence of the compound, the chaperone protein sterically occludes the target protein and prevents interaction with affiliated proteins required for propagating oncogenic signals.

Figure 17: KRAS^{G12C}(ON) inhibitor RM-009 drives formation of a tri-complex binding to an induced pocket at the interface between KRAS^{G12C}(ON) and cyclophilin A.



Surface representation of atomic resolution crystal structures of KRAS^{G12C} (loaded with a non-hydrolysable analog of GTP in grey, gamma phosphate shown in yellow) (KRAS^{G12C}(ON), green) and a binary complex of RM-009 (ochre) and cyclophilin A (brown) (a). The shallow, solvent-exposed groove, or “valley,” between the switch I (blue) and switch II (red) regions of KRAS is highlighted. The cyclophilin A-RM-009 binary complex binds to KRAS^{G12C}(ON) to form a tri-complex (b) with RM-009 bound in an induced binding pocket at the interface between the two proteins, visible following digital removal of the ligand (c).

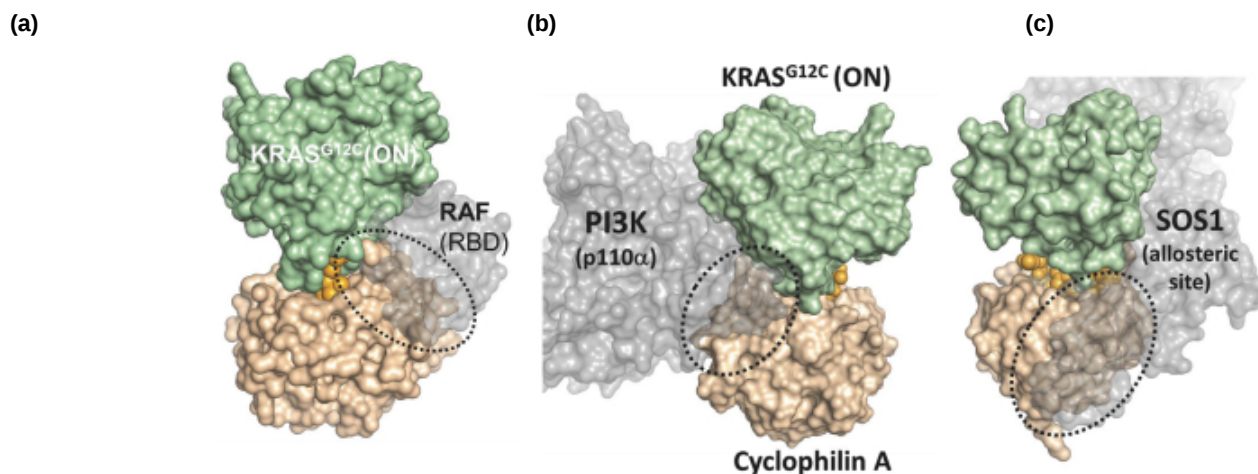
We design and synthesize novel RAS(ON) inhibitors that enter a cell and bind to the highly abundant chaperone protein cyclophilin A to create a “binary complex.” This binary complex presents a unique surface that has the molecular features needed to engage the RAS mutant of interest in a “tri-complex” with the inhibitor sandwiched in an induced binding pocket at the interface between the two proteins. This tri-complex is held together by chemical interactions between cyclophilin A and the respective RAS(ON) mutant and between the compound and each of the two proteins. In some instances, including in the case of cysteine-containing RAS mutants, our RAS(ON) inhibitors can form a covalent bond with RAS. We use our structure-based drug discovery capabilities to drive rational design and optimization of tri-complex inhibitors of RAS(ON).

Our RAS(ON) inhibitor programs

We are initially prioritizing four mutant RAS(ON) targets—KRAS^{G12C}, KRAS^{G13C}, KRAS^{G12D} and NRAS^{G12C}. We believe our tri-complex RAS inhibitors can act in three ways to suppress growth signaling: (1) we have demonstrated direct disruption of the critical RAS-RAF interaction that triggers the downstream portion of the growth signaling cascade. By extension, our RAS(ON) inhibitors likely also: (2) directly disrupt the RAS-PI3K interaction that stimulates mTOR-dependent growth signaling, and (3) prevent the binding of RAS to a recognized allosteric site of SOS1, thereby blocking a positive feedback loop that amplifies conversion of RAS(OFF) to RAS(ON). The

first two effects represent direct suppression of oncogenic RAS signaling. The third effect may attenuate the ability of RAS(ON) to increase GTP-bound levels of other *non-mutant* forms, i.e. wild-type, of RAS in the same cancer cells that may contribute to overall cell survival and proliferation.

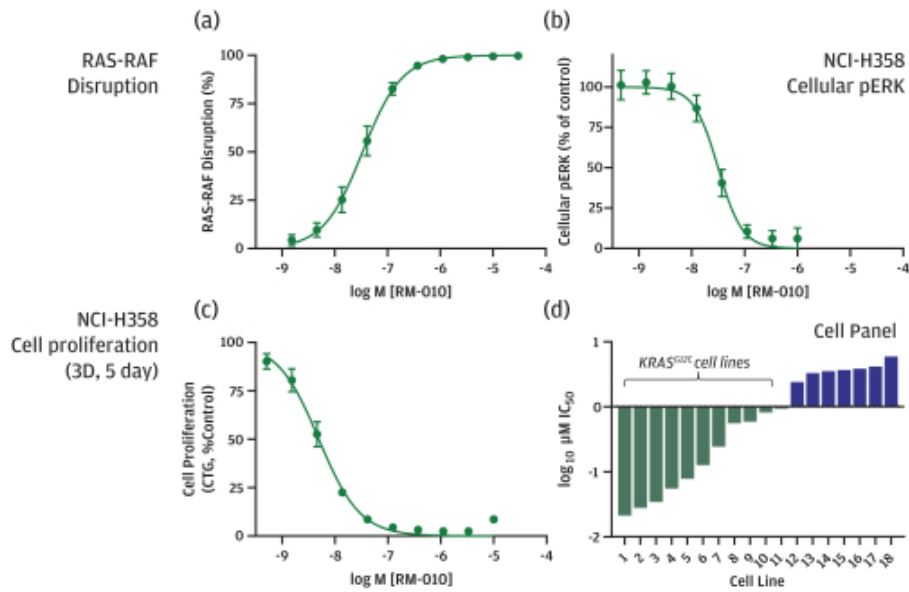
Figure 18: Layered structural models illustrating potential for tri-complex KRAS^{G12C}(ON) inhibitors to sterically preclude engagement of RAF, PI3K and SOS1 by KRAS^{G12C}(ON).



Surface representation of atomic resolution crystal structures of tri-complex of RM-009 with KRAS^{G12C}(ON) with structural overlays showing (in grey) interaction with (a) RAS binding domain (RBD) of BRAF, (b) p110^α catalytic subunit of PI3K and (c) allosteric site on SOS1.

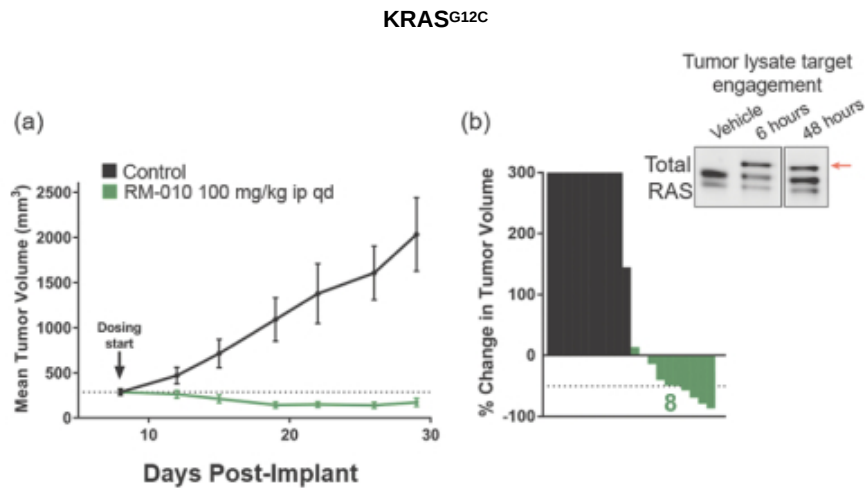
A representative KRAS^{G12C}(ON) tri-complex inhibitor causes concentration-dependent disruption of the interaction between KRAS^{G12C}(ON) and RAF-binding domain of BRAF (Figure 18). This inhibitor also penetrates KRAS^{G12C} mutant tumor cells and potently suppresses pERK levels and cell growth. Most tumor cells carrying this RAS variant are highly sensitive to the inhibitor, whereas none of those with mutations elsewhere in the pathway are sensitive to this inhibitor at pharmacologically relevant concentrations. We believe the range of sensitivities reflects the level of addiction of each specific cell line to KRAS^{G12C}(ON). *In vivo* administration of a representative KRAS^{G12C}(ON) tri-complex inhibitor (RM-010) drives tumor regressions in a KRAS^{G12C} tumor model following repeat dosing (Figure 19). Covalent cross-linking of RAS in the tumor, consistent with KRAS^{G12C} target engagement by this KRAS^{G12C}(ON) tri-complex inhibitor could be observed following administration of a single dose (Figure 20 inset). Anti-tumor activity with another KRAS^{G12C}(ON) tri-complex inhibitor was observed in multiple KRAS^{G12C} tumor models, as demonstrated by RM-015, which drove deep tumor regressions in preclinical xenograft models of both NSCLC and PDAC tumors harboring KRAS^{G12C} (Figure 21).

Figure 19: KRAS^{G12C}(ON) tri-complex inhibitor disrupts KRAS^{G12C}-RAF interaction; inhibits RAS pathway and proliferation *in vitro* in cells bearing KRAS^{G12C} mutation.



Biochemical characterization of the effect of KRAS^{G12C}(ON) tri-complex inhibitor RM-010 on the interaction between KRAS^{G12C} (loaded with a non-hydrolysable analog of GTP) and the RAS binding domain (RBD) of BRAF was performed using a TR-FRET assay (RAS-RAF disruption) (a). RAS pathway activity and cell proliferation in NSCLC NCI-H358 KRAS^{G12C} cells were monitored in 2D cell cultures using levels of ERK1/2 phosphorylation at Thr202/Tyr204 (cellular pERK) (b) and in 3D cell cultures using CellTiter-Glo CTG (cell proliferation) (c). RM-007 potency (expressed as the IC₅₀ in μM) for inhibition of proliferation of a panel of cell lines bearing KRAS^{G12C} mutations (green bars) or other non-KRAS^{G12C} mutations in the RAS pathway (blue bars) (d). Data shown in Figures a, b and c represent the mean of at least two independent studies, each performed in duplicate (error bars show the standard deviation). Data in Figure d are from a single study performed in triplicate.

Figure 20: Tri-complex KRAS^{G12C}(ON) inhibitor suppresses tumor growth in preclinical xenograft model of tumors harboring KRAS^{G12C}

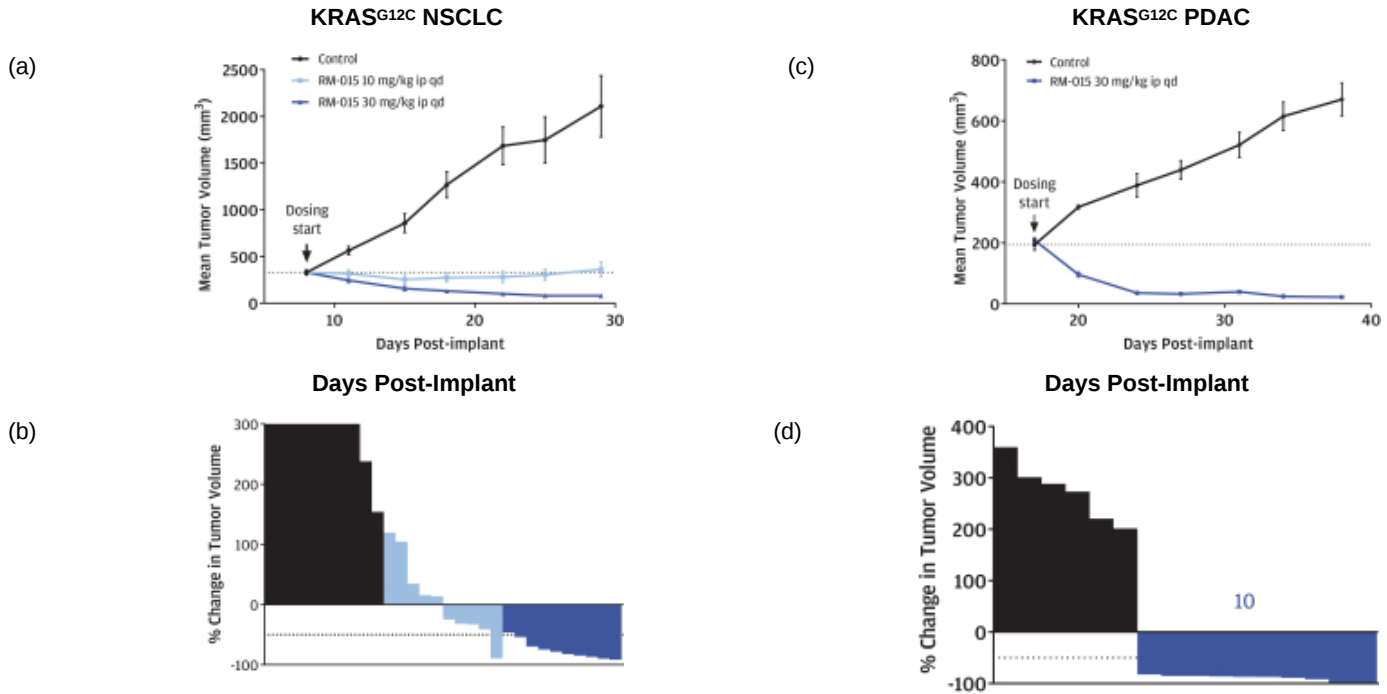


Anti-tumor activity of RM-010 (100 mg/kg, intraperitoneal, daily; ip qd) in NSCLC CDX NCI-H358 KRAS^{G12C} xenograft model in mice. Data represent mean tumor volume over time (a) or waterfall plot of individual end of study responses, with tumor volume expressed as a percentage of initial tumor volume at time of

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study start (truncated at 300%) (b). Number of mice per group = 10. In (a) data represent mean and errors bars represent standard error of the mean. In (b) each animal is represented as a separate bar. Numbers indicate number of regressions (defined as > 10% reduction in tumor volume from starting volume) in each group. Inset, western blot for RAS in tumor lysates prepared from tumors harvested at 6 and 48 hours after administration of a single dose of RM-010 (100 mg/kg, ip) or vehicle to mice bearing NCI-H358 tumors. Data shown are from a single mouse (similar target engagement data were obtained using tumor samples from two additional mice at each time point shown, as well as from three additional mice treated for 24 hours).

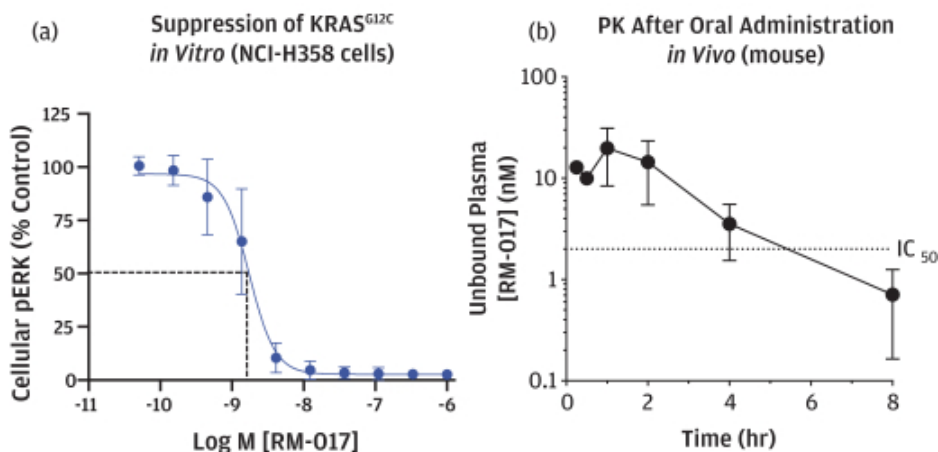
Figure 21: Tri-complex KRAS^{G12C}(ON) inhibitor drives tumor regressions in preclinical xenograft models of NSCLC and PDAC tumors harboring KRAS^{G12C}.



Anti-tumor activity of RM-015 (10 or 30 mg/kg, intraperitoneal, daily; ip qd) in NSCLC CDX NCI-H358 KRAS^{G12C} (a and b) and PDAC CDX NCI-H358 KRAS^{G12C} (c and d) xenograft models in mice. Data represent mean tumor volume over time (a and c) or waterfall plots of individual end of study responses, with tumor volume expressed as a percentage of initial tumor volume at time of study start (truncated at 300% in b) (b and d). Number of mice per group = 10. In (a) and (c) data represent mean and errors bars represent standard error of the mean. In (b) and (d) each animal is represented as a separate bar. Numbers indicate number of regressions (defined as > 10% reduction in tumor volume from starting volume) in each group.

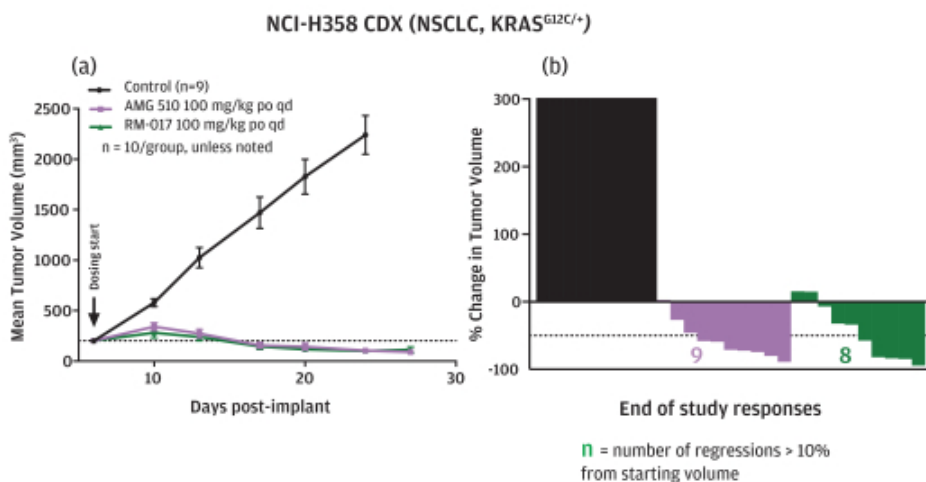
More recent compounds have been developed with oral bioavailability in rodents. Following oral administration, these compounds are able to achieve plasma concentrations that exceed, for several hours, the IC₅₀ for RAS pathway inhibition in cell culture assays (Figure 22). Repeated once daily dosing induces tumor regressions in a KRAS^{G12C} NSCLC mouse xenograft model that are similar to those observed for the equivalent dose of AMG 510, a KRAS^{G12C}(OFF) inhibitor (Figure 23). Given the short duration of dosing and the high sensitivity of the NCI-H358 model to AMG 510, it was not anticipated that the KRAS^{G12C}(ON) inhibitor would show superiority over KRAS^{G12C}(OFF) inhibitors in this model despite significant benefits observed in various *in vitro* comparisons of RAS(ON) and RAS(OFF) inhibitors, as described in this prospectus. Lead optimization activities are focused on further improvements in potency and PK properties.

Figure 22: RAS pathway inhibition *in vitro* and pharmacokinetic profile *in vivo* of RM-017, a potent orally bioavailable KRAS^{G12C}(ON) inhibitor from lead optimization series



(a) RM-017 inhibits RAS pathway activity in NSCLC NCI-H358 KRAS^{G12C} cells. Levels of ERK1/2 phosphorylation at Thr202/Tyr204 (cellular pERK) in 2D cell culture were monitored following incubation with RM-017 for four hours. Data shown represent the mean of at least four independent studies, each performed in duplicate (error bars show the standard deviation). Dotted lines indicate concentration required for inhibition of pathway activation by 50% (IC₅₀). **(b)** Unbound plasma concentration over time profile for RM-017 following oral administration of a single dose at 100 mg/kg to naïve mice. Data represent mean and errors bars represent standard error of the mean. Number of mice per group = 3. Dotted line represents the *in vitro* IC₅₀ (2 nM) for inhibition of pathway activation by RM-017 in NCI-H358 cells (as shown in panel (a)).

Figure 23: Anti-tumor activity of RM-017 dosed orally once daily in a KRAS^{G12C} NSCLC xenograft model.

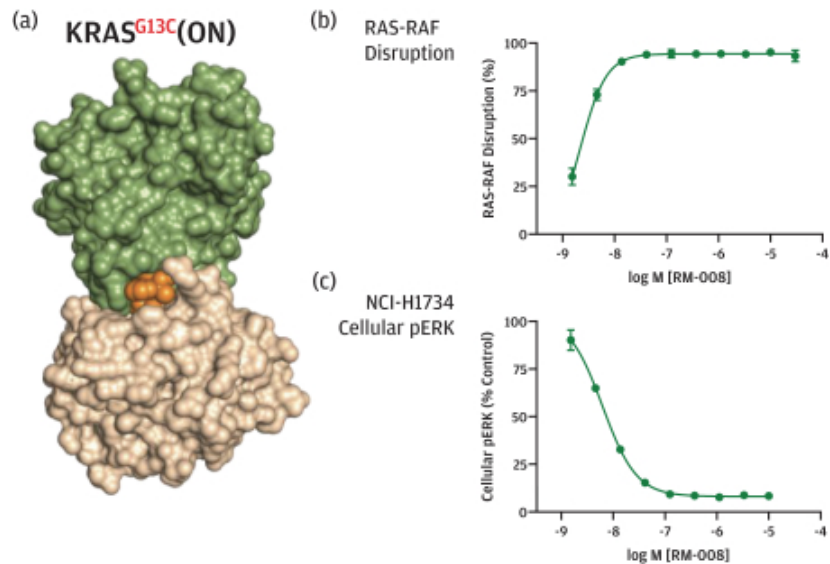


Anti-tumor activity of RM-017 (100 mg/kg, oral, daily; po qd) or AMG 510 (100 mg/kg po qd) in NSCLC CDX NCI-H358 KRAS^{G12C} xenograft model in immune-deficient mice. Data represent mean tumor volume over time **(a)** or waterfall plot of individual end of study responses, with tumor volume expressed as a percentage of initial tumor volume at time of study start (truncated at 300%) **(b)**. Number of mice per group = 10 unless noted. In **(a)** data represent mean and errors bars represent standard error of the mean. In **(b)** each animal is represented as a separate bar. Numbers indicate number of regressions (defined as > 10% reduction in tumor volume from starting volume) in each group.

We are also able to leverage our findings with KRAS^{G12C}(ON) more broadly to facilitate identification of selective tri-complex inhibitors of other RAS(ON) mutants. We are developing inhibitors of several "hotspot" RAS(ON) mutants, with KRAS^{G13C}, KRAS^{G12D}, and NRAS^{G12C} as particular priorities. We have identified compounds with functional activity in biochemical and cellular assays that measure RAS signaling pathway activity and have

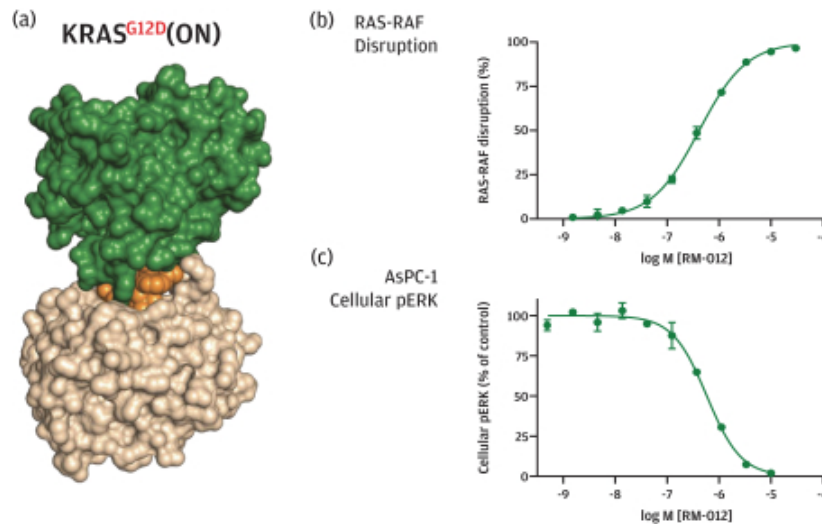
representative data for all of these variants (Figures 22, 23 and 24). We have the ability to target different RAS isoforms (i.e., isoform hopping), such as KRAS and NRAS, different mutational hotspots (i.e., hotspot hopping), such as G12 and G13, and different amino acid residues at a given hotspot (i.e., residue hopping), as exemplified by G12C and G12D. We use a common inhibitory mechanism that underscores the versatility of our tri-complex technology platform. Employing this technology, we have the opportunity to generate a broad portfolio of novel RAS(ON) inhibitors with potentially differentiated clinical profiles for use by patients with different tumor genotypes.

Figure 24: KRAS^{G13C}(ON) tri-complex inhibitor RM-008 disrupts KRAS^{G13C}-RAF interaction and inhibits RAS pathway activity *in vitro* in cells bearing KRAS^{G13C} mutation.



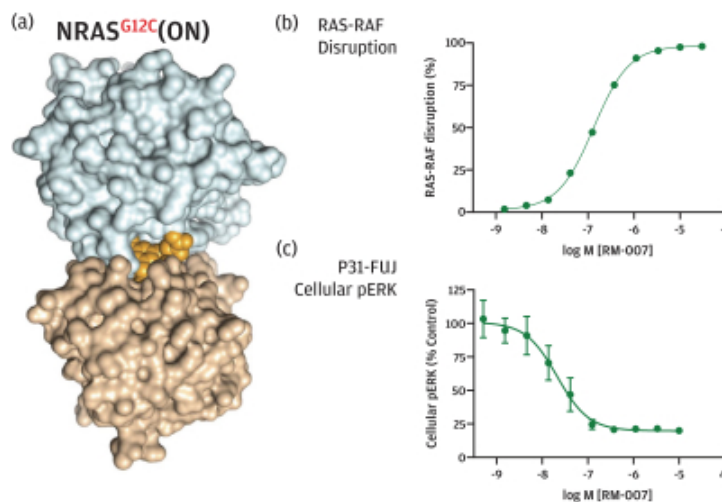
Surface representation of atomic resolution crystal structure of tri-complex of RM-008 with KRAS^{G13C} (loaded with a non-hydrolysable analog of GTP) and cyclophilin A (a). Biochemical characterization of the effect of KRAS^{G13C}(ON) tri-complex inhibitor RM-008 on the interaction between KRAS^{G13C} (loaded with a non-hydrolysable analog of GTP) and the RAS binding domain (RBD) of BRAF was performed using a TR-FRET assay (RAS-RAF disruption) (b). RAS pathway activity in NSCLC NCI-H1734 KRAS^{G13C} cells was monitored in 2D cell cultures using levels of ERK1/2 phosphorylation at Thr202/Tyr204 (cellular pERK) (c). Data shown in Figures b and c represent the mean of duplicate determinations (error bars show the standard deviation) from a single study. Data are representative of at least two independent studies, each performed in duplicate.

Figure 25: KRAS^{G12D}(ON) tri-complex inhibitor RM-012 disrupts KRAS^{G12D}-RAF interaction and inhibits RAS pathway activity *in vitro* in cells bearing KRAS^{G12D} mutation.



Surface representation of atomic resolution crystal structure of tri-complex of RM-012 with KRAS^{G12D} (loaded with a non-hydrolysable analog of GTP) and cyclophilin A (a). Biochemical characterization of the effect of KRAS^{G12D} (ON) tri-complex inhibitor RM-012 on the interaction between KRAS^{G12D} (loaded with a non-hydrolysable analog of GTP) and the RAS binding domain (RBD) of BRAF was performed using a TR-FRET assay (RAS-RAF disruption) (b). RAS pathway activity in pancreatic AsPC-1 KRAS^{G12C} cells was monitored in 2D cell cultures using levels of ERK1/2 phosphorylation at Thr202/Tyr204 (cellular pERK) (c). Data shown in Figures b and c represent the mean of duplicate determinations (error bars show the standard deviation) from a single study. Data in Figure c representative of at least two independent studies, each performed in duplicate.

Figure 26: NRAS^{G12C}(ON) tri-complex inhibitor RM-007 disrupts NRAS^{G12C}-RAF interaction; inhibits RAS pathway activity *in vitro* in cells bearing NRAS^{G12C} mutation.

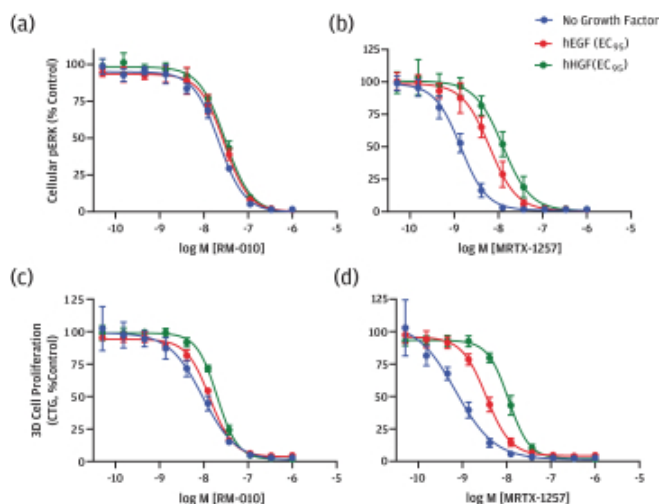


Surface representation of atomic resolution crystal structure of tri-complex of RM-007 with NRAS^{G12C} (loaded with a non-hydrolysable analog of GTP) and cyclophilin A (a). Biochemical characterization of the effect of NRAS^{G12C} (ON) tri-complex inhibitor RM-007 on the interaction between NRAS^{G12C} (loaded with a non-hydrolysable analog of GTP) and the RAS binding domain (RBD) of BRAF was performed using a TR-FRET assay (RAS-RAF disruption) (b). RAS pathway activity in AML P31-FUJ NRAS^{G12C} cells was monitored in 2D cell cultures using levels of ERK1/2 phosphorylation at Thr202/Tyr204 (cellular pERK) (c). Data shown in Figure b represent the mean of duplicate determinations (error bars show the standard deviation) from a single study. Data are representative of at least two independent studies, each performed in duplicate. Data shown in Figure c represent the mean of two independent studies, each performed in duplicate (error bars show the standard deviation).

Reduced susceptibility of RAS(ON) inhibitors to adaptive resistance mechanisms, such as RTK activation

In tumor cells that are addicted to high levels of RAS activation, we believe that selective inhibitors of RAS(ON) will suppress cell growth and survival and be less susceptible to adaptive resistance mechanisms recognized for RAS(OFF) inhibitors, specifically the KRAS^{G12C}(OFF) inhibitors that are currently in early clinical development. KRAS^{G12C}(OFF) inhibitors are susceptible to any cellular perturbations that reduce the intracellular pool of KRAS(OFF). Central to the differentiated profile of KRAS^{G12C}(ON) inhibitors is their relative insensitivity to cellular mechanisms that activate KRAS^{G12C} and thereby increase the pool of KRAS^{G12C}(ON) and decrease the pool of KRAS(OFF). We have demonstrated that the addition of growth factors to cells in order to directly activate RTKs (and hence increase the RAS(ON) pool) reduces the cellular potency of KRAS^{G12C}(OFF) inhibitors but has much less effect on cellular potency of KRAS^{G12C}(ON) inhibitors (Figure 27). These findings corroborate a previous published report that KRAS^{G12C} target engagement by a representative KRAS^{G12C}(OFF) inhibitor is significantly reduced by growth factor administration, consistent with the relative depletion of the therapeutic target.

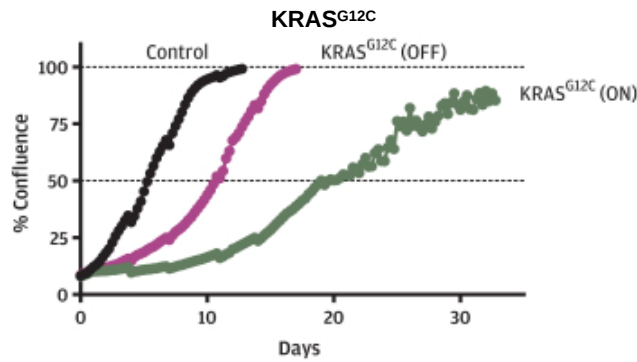
Figure 27: Differential susceptibility of KRAS^{G12C}(ON) and KRAS^{G12C}(OFF) inhibitors to the effects of RTK activation, via growth factor challenge, on inhibition of RAS pathway and cell proliferation *in vitro*.



RAS pathway activity and cell proliferation in NSCLC NCI-H358 KRAS^{G12C} cancer cells were monitored in 2D cell cultures using levels of ERK1/2 phosphorylation at Thr202/Tyr204 after 4 hours of compound incubation (a and b) and in 3D cell cultures using CellTiter-Glo (CTG) after 5 days of compound incubation (c and d). The effects of activation of EGFR and MET receptor, by addition of growth factor ligands human EGF (hEGF) and human HGF (hHGF) (at their EC₉₅ concentrations) respectively, on the inhibitory potency of the KRAS^{G12C}(ON) inhibitor RM-010 (a and c) and KRAS^{G12C}(OFF) inhibitor, MRTX1257 (b and d) is shown. Data shown in Figures a, b, c and d represent the mean of two independent studies, each performed in duplicate (error bars show the standard deviation).

Furthermore, using long-term proliferation studies *in vitro* to monitor cell proliferation over time, and by extension the durability of inhibitor effect, we have shown that the KRAS^{G12C}(ON) inhibitors produce more durable growth inhibition compared to KRAS^{G12C}(OFF) inhibitors (Figure 28). These data highlight the relative insensitivity of KRAS^{G12C}(ON) inhibitors *in vitro* to activation of adaptive resistance mechanisms, such as RTK activation, which can be exploited by a tumor cell in response to suppression of the RAS signaling pathway. We believe these findings may be clinically relevant since the durability of response to RAS signaling pathway inhibitors is generally accepted to be a key factor impacting anti-tumor activity.

Figure 28: Effects of tri-complex KRAS^{G12C}(ON) inhibitor or KRAS^{G12C}(OFF) inhibitors on long term cell growth *in vitro*.

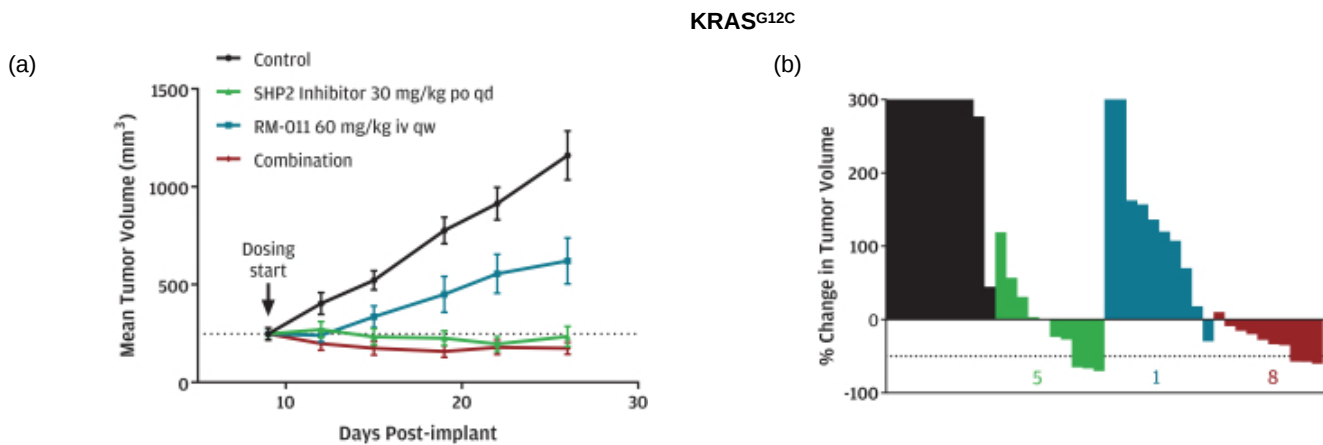


NSCLC NCI-H358 KRAS^{G12C} cancer cells were maintained in 2D cell culture and cell proliferation (expressed as % confluence) monitored over time using the Incucyte imaging platform. Cells were incubated in the absence (control, black) or presence of KRAS^{G12C}(OFF) (purple) or KRAS^{G12C}(ON) (green) inhibitors at equi-efficacious concentrations, that is concentrations that produced 75% inhibition of proliferation in short-term growth studies. Under control conditions cells reached 100% confluence within ~ 10 days. Addition of the KRAS^{G12C}(OFF) inhibitor tool compound, Mirati-11, inhibited cell growth, evident as an ~ 2-fold delay in the time to reach confluence (~ 20 days). In contrast, a representative KRAS^{G12C}(ON) inhibitor (RM-007) caused a more sustained suppression of cell proliferation and confluence was not achieved during the time course of the experiment (~ 35 days). Data are from a single experiment, similar data have been obtained in another independent study.

Combination strategy for KRAS^{G12C}(ON) inhibitors

The use of dual and even triple combination regimens to overcome adaptive resistance mechanisms to inhibitors of the RAS signaling pathway is well established based on clinical observations. We and others have demonstrated that robust combination benefit can be conferred in human cancer cell line xenograft models *in vivo* by combining a SHP2 inhibitor with a KRAS^{G12C}(OFF) inhibitor. Using the long-term proliferation model, we observed robust combination benefit *in vitro* from combining a SHP2 inhibitor and a KRAS^{G12C}(ON) inhibitor. While the molecular mechanism(s) underlying this combinatorial benefit has not been fully established, the combination of SHP2 inhibition and KRAS^{G12C}(ON) inhibitor does demonstrably increase apoptosis, or programmed cell death, in a KRAS^{G12C} cell line *in vitro*. Combination benefit was also observed *in vivo* for a SHP2 inhibitor and a KRAS^{G12C}(ON) inhibitor (Figure 29).

Figure 29: Combination benefit for tri-complex KRAS^{G12C}(ON) inhibitor and SHP2 inhibitor in preclinical xenograft model of tumors harboring KRAS^{G12C} mutations.



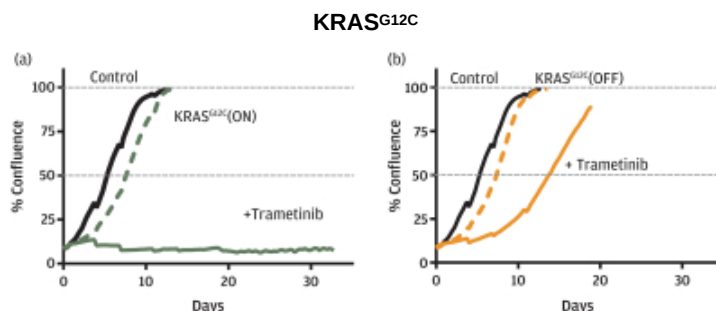
Anti-tumor activity of RM-011 (60 mg/kg, intravenous, once weekly; iv qw) and SHP2 inhibitor (RMC-4550) (30 mg/kg, oral, daily; po qd) as single agents or in combination in NSCLC CDX NCI-H358 KRAS^{G12C} xenograft model in mice. Data represent tumor volume over time (a) or waterfall plot of individual end of study responses.

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with tumor volume expressed as a percentage of initial tumor volume at time of study start (truncated at 300%) (b). Number of mice per group = 10. In (a) data represent mean, errors bars represent standard error of the mean. In (b) each animal is represented as a separate bar. Numbers indicate number of regressions (defined as > 10% reduction in tumor volume from starting volume) in each group.

Another rational combination partner for a KRAS^{G12C}(ON) inhibitor is a MEK inhibitor. In the long-term *in vitro* proliferation model, dramatic combination benefit was demonstrated for a MEK inhibitor (trametinib) and a KRAS^{G12C}(ON) inhibitor (Figure 30). Complete and sustained inhibition of cell growth and substantial cell death were observed. These effects are in contrast to the relatively rapid escape observed with the combination of a KRAS^{G12C}(OFF) inhibitor and trametinib, in which cells reached full confluence within 20 days.

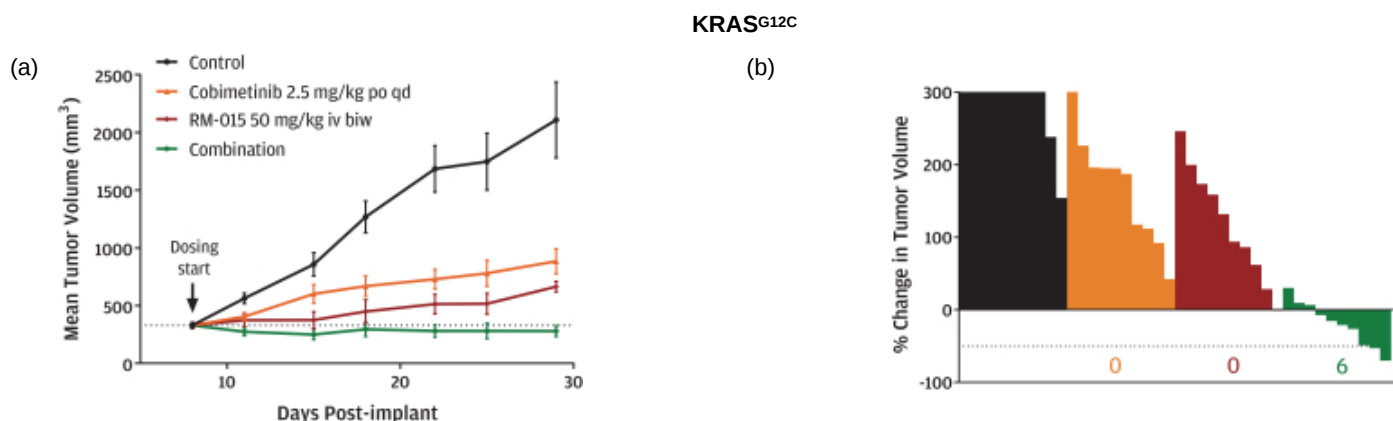
Figure 30: Effects of tri-complex KRAS^{G12C}(ON) inhibitor or KRAS^{G12C}(OFF) inhibitor alone and in combination with MEK inhibitor, trametinib, on long term cell growth *in vitro*.



NSCLC NCI-H358 KRAS^{G12C} cancer cells were maintained in 2D cell culture and cell proliferation (expressed as % confluence) monitored over time using the Incucyte imaging platform. Cells were incubated in the absence (control, black) or presence of an EC₅₀ concentration of test articles. **(a)** Addition of KRAS^{G12C}(ON) inhibitor (RM-007, dotted green line) produced a modest delay in the time for cells to reach 50% confluence, but the simultaneous addition of an EC₅₀ concentration of the MEK inhibitor trametinib (solid green line) caused complete inhibition of cell growth and no viable cells were apparent during the time course of the experiment (~ 35 days). **(b)** Addition of a KRAS^{G12C}(OFF) inhibitor (Mirati-11, orange dotted line) produced a similar modest delay in the time for cells to reach 50% confluence and although the simultaneous addition of trametinib (solid orange line) caused a slight delay in cell proliferation, indicative of an initial combinatorial benefit, the cells escaped relatively quickly and approached full confluence within ~20 days. Data are from a single experiment, similar data have been obtained in another independent study.

These results can be interpreted within the framework of what is known regarding the mechanism of action of the respective compounds and their effects on RAS signaling pathway activity. Hyperactivation of RTKs accompanied by reactivation of RAS is a well-established response to MEK (or ERK) inhibition, reflecting relief of endogenous inhibitory feedback loops in the presence of the downstream inhibitor. Consistent with this hypothesis, others have shown that MEK inhibition reduces KRAS^{G12C} target engagement by a representative KRAS^{G12C}(OFF) inhibitor. In contrast, MEK inhibitor-induced activation of RAS does not antagonize the activity of a compound that inhibits KRAS^{G12C}(ON) directly; rather, in this context the complementary mechanisms of the two agents can drive maximal pathway inhibition, which manifests as cell death.

We also observed combination benefit for a KRAS^{G12C}(ON) inhibitor and a MEK inhibitor *in vivo* in a preclinical xenograft model of tumors harboring KRAS^{G12C} mutations (Figure 31).

Figure 31: Combination benefit for tri-complex KRAS^{G12C}(ON) inhibitor and MEK inhibitor in preclinical xenograft model of tumors harboring KRAS^{G12C} mutations.

Anti-tumor activity of RM-015 (50 mg/kg, intravenous, twice weekly; iv biw) and MEK inhibitor (cobimetinib) (2.5 mg/kg, oral, daily; po qd) as single agents or in combination in NSCLC CDX NCI-H358 KRAS^{G12C} xenograft model in mice. Data represent tumor volume over time (a) or waterfall plot of individual end of study responses, with tumor volume expressed as a percentage of initial tumor volume at time of study start (truncated at 300%) (b). Number of mice per group = 10. In (a) data represent mean, errors bars represent standard error of the mean. In (b) each animal is represented as a separate bar. Numbers indicate number of regressions (defined as > 10% reduction in tumor volume from starting volume) in each group.

Drug discovery, optimization and development strategy

Initially, we intend to prioritize four mutant RAS(ON) targets in our drug discovery efforts—KRAS^{G12C}, KRAS^{G13C}, KRAS^{G12D}, and NRAS^{G12C}. Our current RAS(ON) drug discovery programs are in either a lead generation or lead optimization stage.

Similarly to “Rule of 5” drug discovery programs in the lead generation stage, in the lead generation stage for our RAS(ON) targets, we prosecute iterative cycles of compound design, synthesis and testing in various assays to identify specific chemical features that contribute to desired characteristics, such as potent and durable inhibition of the target, selectivity for the target of interest, physicochemical properties (for example, solubility) that support formulation, *in vivo* ADME (absorption, distribution, metabolism and excretion), intrinsic chemical stability, and tolerability *in vivo*. The lead optimization stage for our RAS(ON) targets involves further iterative cycles of compound design, synthesis and testing toward the goal of bringing these features together in individual compounds to meet development candidate profiles. As compounds advance through this process, they undergo progressive scrutiny through extensive preclinical tests both *in vitro* and *in vivo*, culminating in development candidate selection followed by IND-enabling studies conducted in accordance with regulatory guidelines.

These iterative design-make-test cycles can be more challenging for complex “Beyond Rule of 5” small molecules such as our tri-complex inhibitors, and we have developed tools, processes and know-how to support practical drug discovery of these types of molecules. As for conventional “Rule of 5” drug discovery programs, our compounds produced during lead generation or optimization stages are expected to have a diverse range of properties. Some of these compounds will not meet our candidate profile and will be rejected while others will fulfill some of the characteristics of our candidate profile, and the features of such compounds will be retained

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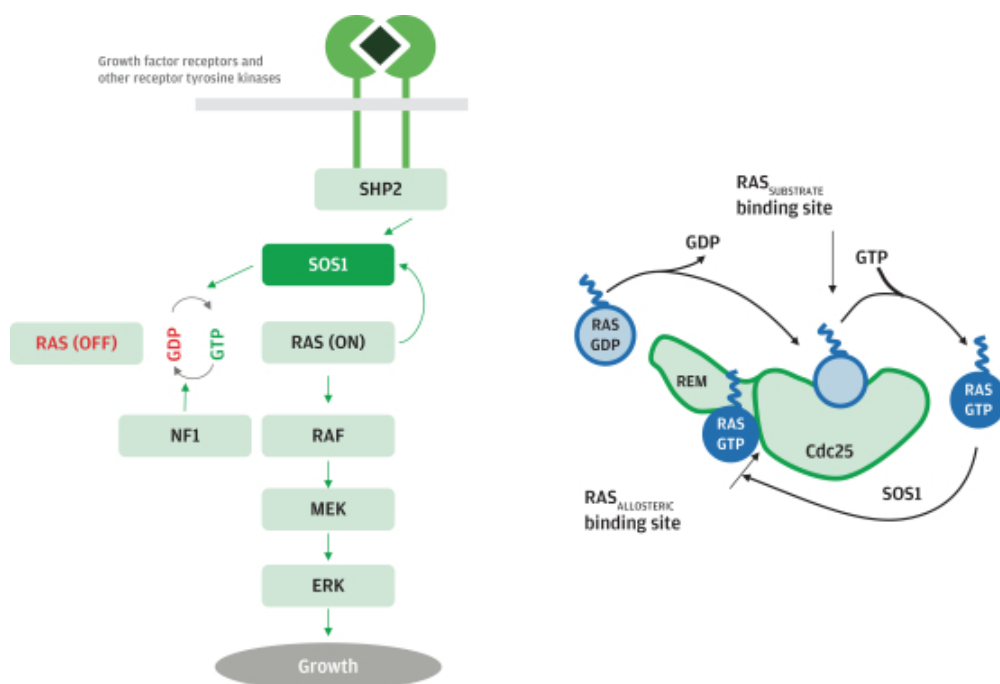
where possible. To date approximately 2,000 different test compounds have been produced and characterized in various *in vitro* assays, with a subset of these characterized *in vivo* in rodents. The compounds reported in Figures 20, 21, 27 and 29 are examples of tri-complex KRAS(ON) inhibitors that have demonstrated *in vivo* anti-tumor activity in xenograft models of human cancers in mice and were generally well-tolerated as indicated by either minimal or no body weight loss and an absence of observable gross abnormalities in these studies. We have also identified compounds with unfavorable properties such as low *in vitro* potency for KRAS^{G12C}(ON), cross-reactivity with one or more well-known safety targets, low solubility, poor ADME properties, including lack of oral bioavailability, and poor tolerability. Adverse effects have been observed following administration of high doses of some compounds to rodents by one or more routes of administration. As these effects were seen with only certain compounds and did not extend across all studies, doses or routes of administration, we do not believe there is a generalized liability of the tri-complex platform or chemical scaffolds underlying our RAS(ON) inhibitor programs.

We believe our multiparameter optimization efforts will yield candidates that meet our development candidate profiles to be advanced into IND-enabling studies and clinical studies as appropriate and we expect to nominate our first RAS(ON) development candidate in 2020.

Our SOS1 program

The SOS1 protein is responsible for stimulating the conversion of RAS from the inactive GDP-bound form (RAS(OFF)) to the active GTP-bound form (RAS(ON)) in response to growth factor receptor signaling. SOS1 directly activates RAS proteins by promoting the release of the bound GDP and thereby facilitating the binding of GTP, which is present within a cell in great excess to GDP, to generate RAS(ON). SOS1 itself is activated by RAS through the binding of RAS(ON) to an allosteric site on the SOS1 protein (Figure 32). As a result, there is a positive feedback loop between SOS1 and RAS that increases RAS signaling. The activation of RAS by SOS1 is “processive”; that is, once a single molecule of SOS1 is activated it can sequentially activate multiple RAS molecules. As a result, the potential for amplification of RAS signals by SOS1 is considerable. Therefore, we believe that inhibition of SOS1 may represent a viable approach for targeting RAS-driven tumors.

Figure 32



We have designed and synthesized a number of potent and selective inhibitors of SOS1. The current focus of our lead optimization stage program is to improve the potency and drug-like properties of compounds in this series. We are investigating the potential utility of SOS1 inhibitors alone and in combination with our other proprietary inhibitors of RAS signaling, such as our SHP2 inhibitors and mutant-selective RAS(ON) inhibitors, in a wide range of *in vitro* and *in vivo* models of genetically-defined cancers that are addicted to the RAS signaling pathway.

Our 4EBP1/mTORC1 program

Overview

mTORC1 is a critical regulator of metabolism, growth and proliferation within cells, including cancer cells. The abnormal activation of mTORC1, and subsequent inactivation of the tumor suppressor 4EBP1, is a mechanism that is frequently harnessed by cancer cells to gain a growth and proliferation advantage over normal cells. Our preclinical development candidate, RMC-5552, selectively and deeply inhibits mTORC1, thereby preventing phosphorylation and inactivation of 4EBP1, a downstream protein in the mTOR signaling pathway that normally suppresses expression of certain oncogenes such as C-MYC. Approximately two-thirds of breast cancers contain oncogenic mutations that hyper-activate mTORC1. We advanced RMC-5552 into IND-enabling development in June 2019.

Preclinical studies

RMC-5552 is a potent and selective inhibitor of mTORC1, that exhibits selectivity over mTORC2 and a broad panel of kinases (Figure 33).

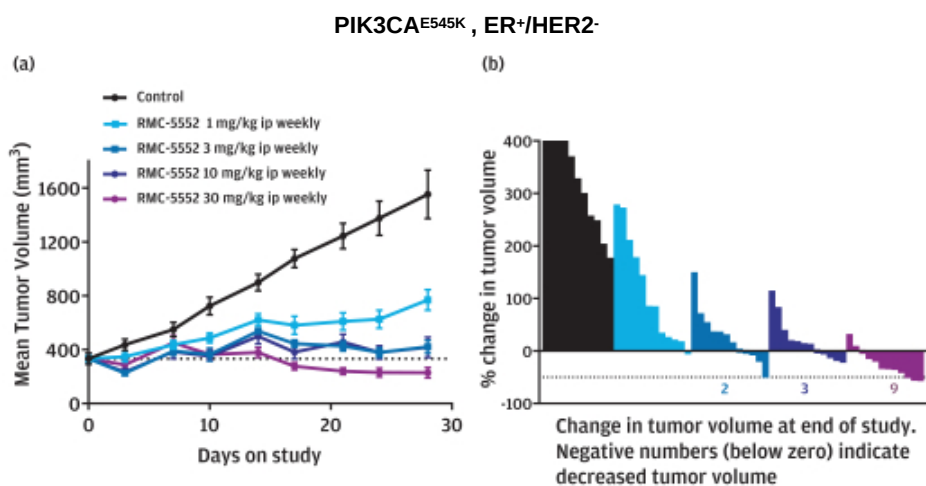
Figure 33: *In vitro* profile of RMC-5552

	RMC-5552
Inhibition of mTORC1: pS6K	0.14 nM
Inhibition of mTORC1: p4EBP1 ¹	0.48 nM
Selectivity over mTORC2: pAKT ²	40X
Selectivity over kinases: e.g., PI3K ²	53X

In vitro potency for RMC-5552 to inhibit phosphorylation of mTORC1 (pS6K and p4EBP1) and mTORC2 (pAKT) substrates was determined in MDA-MB-468 cells. Data represent mean of at least two independent determinations. Selectivity over mTORC2 represents ratio of potency values for inhibition of AKT phosphorylation to inhibition of 4EBP1 phosphorylation. Selectivity over other kinases e.g. PI3K, represents ratio of potency values for inhibition of PI3K-alpha to mTORC1 in a biochemical, synthetic peptide phosphorylation assay. ¹ Rapamycin is not considered an inhibitor of 4EBP1 phosphorylation. ² Active site inhibitors are not considered selective over mTORC2 or other kinases.

In a xenograft model of human breast cancer in which an activating mutation in PIK3CA drives hyperactivation of the mTOR pathway, RMC-5552 inhibited tumor 4EBP1 phosphorylation at 48 hours-post intraperitoneal administration of a 3 mg/kg or 10 mg/kg dose by 71% and 63%, respectively. RMC-5552 induced significant regression of tumors when administered weekly via intraperitoneal injection at doses that were well tolerated (Figure 34). Inhibition of tumor growth was also seen in models of ovarian, liver, bladder and head and neck cancers that collectively bear activating mutations in the mTOR signaling pathway, are addicted to production of oncogenic proteins, and/or are dependent on inactivation or loss of 4EBP1.

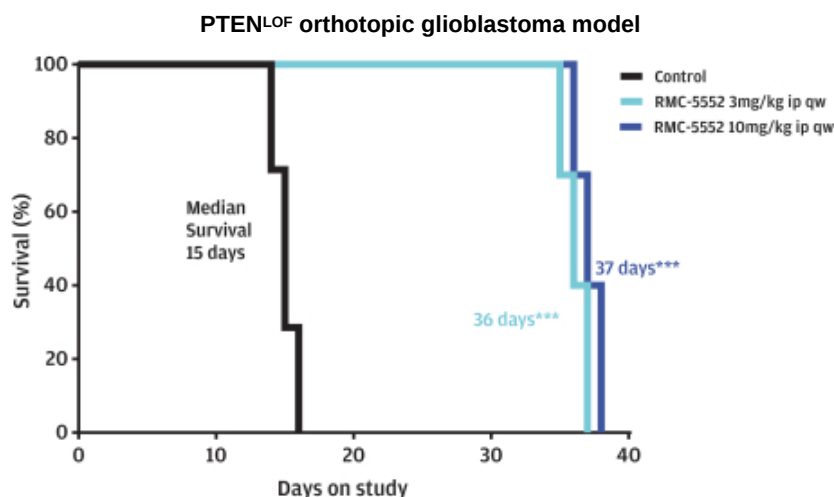
Figure 34: RMC-5552 drives tumor regressions in a preclinical xenograft model of breast cancer tumors harboring PIK3CA mutations.



Once weekly intraperitoneal administration of RMC-5552 (3 mg/kg, 10 mg/kg or 30 mg/kg ip qw) produces a dose-dependent inhibition of tumor growth in breast cancer MCF-7 ER-positive (ER⁺), HER2-negative (HER2⁻), PIK3CA^{E545K} cancer cell line-derived xenograft model in mice. Data represent tumor volume over time (a) and waterfall plots of individual end of study responses with tumor volume expressed as a percentage of initial tumor volume at time of study start (truncated at 400%) (b). Number of mice per group = 12. In (a) data represent mean, errors bars represent standard error of the mean. In (b) each animal is represented as a separate bar. Numbers indicate number of regressions (defined as > 10% reduction in tumor volume from starting volume) in each group. Dotted line in panel (b) references 50% reduction in tumor volume.

We also tested RMC-5552 in the U87 cell line representing a human brain cancer, glioblastoma multiforme (Figure 35). In this model the tumors were implanted directly into the brains of immunodeficient mice to more accurately mimic the human disease. RMC-5552 was tested at two different doses, both of which were given once weekly via intraperitoneal injection. Because of the technical difficulties associated with measuring the size of tumors growing within the cranium, the main outcome measure for this experiment was duration of survival. RMC-5552 was well tolerated and prolonged survival at all doses tested.

Figure 35: RMC-5552 prolongs survival in a preclinical xenograft model of glioblastoma multiforme harboring PTEN^{LOF}.

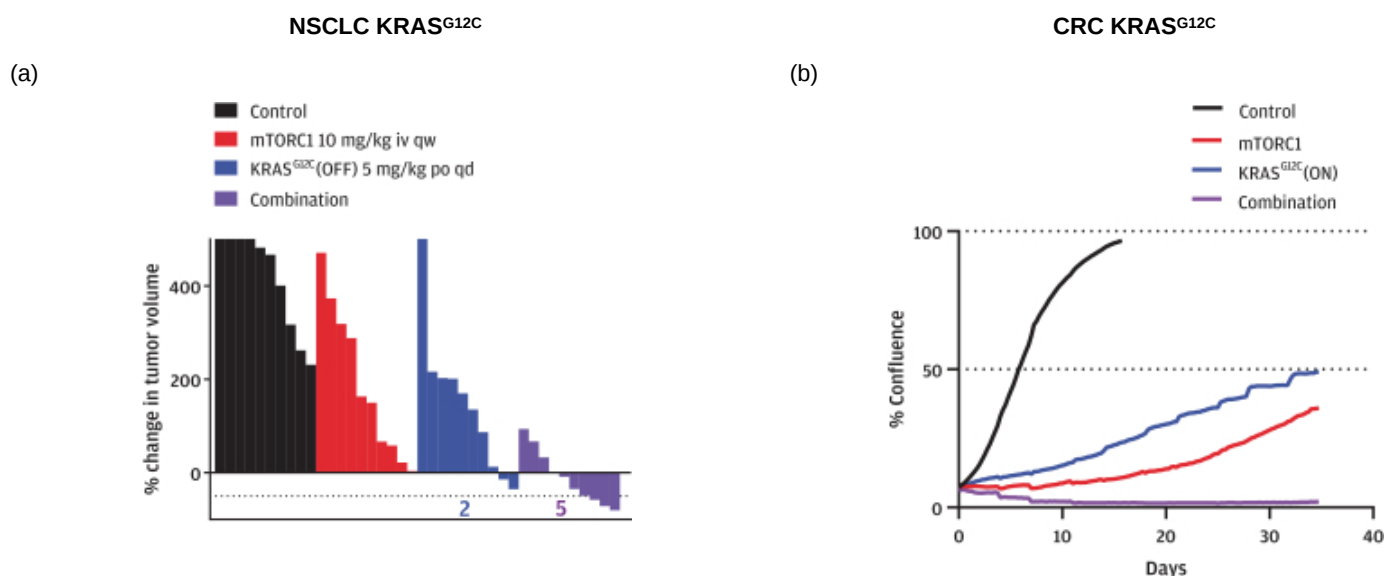


Anti-tumor activity of RMC-5552 (3 mg/kg and 10 mg/kg once weekly intraperitoneal administration, ip qw), in a U87MG-Luc (PTEN^{LOF}) orthotopic glioblastoma model in mice. Data represent Kaplan–Meier curves showing percentage of animals meeting the survival endpoint in each treatment group for the duration of the study, number of animals per group = 10. RMC-5552 (3 mg/kg and 10 mg/kg (ip, qw) is statistically significantly different from control (***p<0.0001, Log-rank test).

As described earlier, RAS-addicted cancer cells can develop adaptive resistance to RAS pathway inhibitors and lose sensitivity to treatment by hijacking other cell signaling circuitry to circumvent the inhibition. In some cases this may involve activation of the mTOR signaling cascade. We have observed combination benefit for an mTORC1 inhibitor with KRAS^{G12C} (ON) and (OFF) inhibitors in preclinical models of NSCLC and CRC cancers harboring KRAS^{G12C} mutations (Figure 36). In particular, STK11 loss-of-function mutations promote activation of mTORC1 and have been found as co-mutations in some human cancers carrying KRAS^{G12C}. In a preclinical NSCLC tumor model harboring both KRAS^{G12C} and STK11 mutations, the combination of a selective bi-steric mTORC1 inhibitor (RM-006) with a KRAS^{G12C}(OFF) inhibitor (AMG 510) induced tumor regressions, although neither compound alone displayed significant anti-tumor activity in this context (Figure 37). Further, STK11 mutations in NSCLC have been reported to be associated with poor clinical outcomes from checkpoint inhibitor (anti-PD1) therapy, highlighting their significance in the pathogenesis of some tumors.

These preclinical data support further evaluation of KRAS^{G12C} inhibitors in combination with RMC-5552, both preclinically and potentially clinically. Based on the strength of our preclinical studies, we advanced RMC-5552 into IND-enabling development in June 2019. We expect to be ready to submit an IND for RMC-5552 in 2020.

Figure 36. Combination benefit for mTORC1 inhibitor with KRAS^{G12C} inhibitors in preclinical models of cancers harboring KRAS^{G12C} mutations.



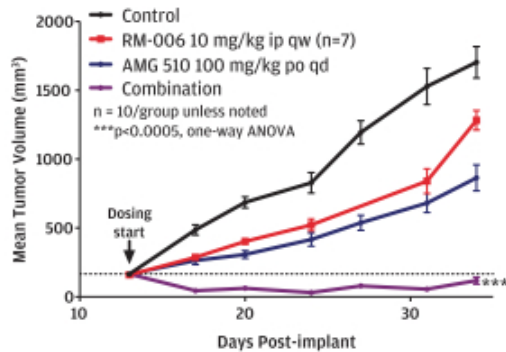
Combination benefit between an mTORC1 inhibitor and KRAS^{G12C} inhibitor was explored in NSCLC (a) and CRC (b) cancer cells harboring KRAS^{G12C} mutations. a) Anti-tumor activity of mTORC1 inhibitor (RM-006 at 10 mg/kg, intravenous, once weekly; iv qw) and KRAS^{G12C}(OFF) inhibitor AMG 510 (5 mg/kg, oral, daily; po qd) as single agents or in combination in NSCLC CDX NCI-H358 KRAS^{G12C} xenograft model in mice. Data represent waterfall plot of individual end of study responses, with tumor volume expressed as a percentage of initial tumor volume at time of study start (truncated at 450%). Number of mice per group = 10. Each animal is represented as a separate bar. Numbers indicate number of regressions (defined as > 10% reduction in tumor volume from starting volume) in each group.

b) CRC SW837 KRAS^{G12C} cancer cells were maintained in 2D cell culture and cell proliferation (expressed as % confluence) monitored over time using the Incucyte imaging platform. Cells were incubated in the absence (control, black) or presence of an mTORC1 inhibitor (RM-006, 10 nM) or KRAS^{G12C}(ON) inhibitor (RM-015, 1 μM). Incubation with the mTORC1 inhibitor (red) or KRAS^{G12C}(ON) inhibitor (blue) alone delayed the time for the cells to reach 50 % confluence. However, the simultaneous addition of the two inhibitors caused complete inhibition of cell growth and no viable cells were apparent during the time course of the experiment (~ 35 days). Data are from a single experiment, similar data have been obtained in another independent study. RM-006 is a proprietary mTORC1 inhibitor tool compound.

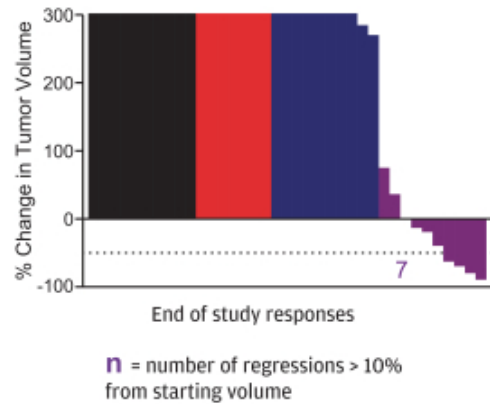
Figure 37: Combination benefit for mTORC1 inhibitor with KRAS^{G12C} inhibitor in a preclinical NSCLC tumor model harboring KRAS^{G12C} plus STK11 mutations

NCI-H2122 NSCLC CDX (KRAS^{G12C}; STK11^{mut})

(a)



(b)



Anti-tumor activity of mTORC1 inhibitor (RM-006 at 10 mg/kg, intraperitoneally, once weekly; ip qw) and KRAS^{G12C}(OFF) inhibitor AMG 510 (100 mg/kg, oral, daily; po qd) as single agents or in combination in NSCLC CDX NCI-H2122 KRAS^{G12C} STK11^{mut} xenograft model in immune-deficient mice. Data represent mean tumor volume over time (a) or waterfall plot of individual end of study responses, with tumor volume expressed as a percentage of initial tumor volume at time of study start (truncated at 300%) (b). Number of mice per group = 10 unless noted. In (a) data represent mean and errors bars represent standard error of the mean. In (b) each animal is represented as a separate bar. Numbers indicate number of regressions (defined as > 10% reduction in tumor volume from starting volume) in each group. RM-006 is a proprietary mTORC1 inhibitor tool compound.

Commercial plan

We intend to retain significant development and commercialization rights to our product candidates and, if marketing approval is obtained, to commercialize our product candidates on our own, or potentially with a partner, in the United States and other regions. Our most advanced product candidate, RMC-4630, is the subject of a global collaboration with Sanofi. Unless otherwise delegated to us by the joint commercialization committee, Sanofi has the sole right and responsibility for all aspects of the commercialization of SHP2 inhibitors in the world for any and all uses, at its expense, subject to our right to elect to co-promote SHP2 inhibitors in the United States. In the United States, we will share equally with Sanofi the profits and losses applicable to commercialization of SHP2 inhibitor products. Sanofi is responsible for manufacturing SHP2 inhibitors for commercial supply and is expected to lead commercialization efforts through a joint commercialization committee representing the partners. We currently have no sales, marketing or commercial product distribution capabilities. We intend to build the necessary infrastructure and capabilities over time for the United States, and potentially other regions, following further advancement of our product candidates. Clinical data, the size of the addressable patient population, the size of the commercial infrastructure and manufacturing needs, and the status of our pipeline, may all influence or alter our commercialization plans.

Collaboration agreement with Sanofi

In June 2018, we entered into a collaborative research, development and commercialization agreement with Aventis, Inc. (an affiliate of Sanofi), or the Sanofi Agreement, to research and develop SHP2 inhibitors, including RMC-4630, for any indications. The Sanofi Agreement was assigned to Genzyme Corporation, a Sanofi affiliate, in December 2018. For the purposes of this discussion, we refer to Genzyme Corporation as Sanofi. Pursuant to the Sanofi Agreement, we granted Sanofi a worldwide, exclusive, sublicensable (subject to our consent in

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certain circumstances) license under certain of our patents and know-how to research, develop, manufacture, use, sell, offer for sale, import and otherwise commercialize SHP2 inhibitors, including RMC-4630, for any and all uses, subject to our exercise of rights and performance of obligations under the Sanofi Agreement. Such intellectual property exclusively licensed to Sanofi includes our interest under any of our solely-owned or jointly-owned inventions arising out of activities undertaken pursuant to the development of SHP2 inhibitor product candidates under the Sanofi Agreement.

Under the Sanofi Agreement, we have primary responsibility for performing preclinical research on SHP2 inhibitors, pursuant to an initial research plan and budget directed toward the identification, validation and optimization of SHP2 inhibitors for 2018-2020. The research plan and budget beyond 2020 will be determined by a joint research and development committee, over which Sanofi has final decision-making power subject to certain exceptions. We have primary responsibility for early clinical development of RMC-4630 pursuant to an initial development plan. The joint research and development committee is responsible for preparing development plans for other SHP2 inhibitors approved by such committee for development, if any. Sanofi is responsible for 80% of all internal and external research costs and expenses incurred under the research plan for 2019 and 2020, and for all other internal and external costs and expenses incurred to perform activities under the research and development plans. We are responsible for 20% of all internal and external research costs incurred under the research plan for 2019 and 2020, in which our share of these costs is estimated to be approximately \$2 million in total, representing less than three percent of the anticipated overall budget for the SHP2 program in 2019 and 2020. Sanofi is responsible for all costs under the development plan, and since our SHP2 program is in clinical development, the costs under the development plan are expected to be significantly greater than the costs under the research plan. We are responsible for the manufacture of SHP2 inhibitors for Phase 1 and non-registrational Phase 2 clinical trials at Sanofi's cost, while Sanofi is responsible for manufacturing SHP2 inhibitors for all other clinical trials and commercial supply. Sanofi has the sole right and responsibility to perform all regulatory activities under the Sanofi Agreement, except with respect to certain trials conducted by us or otherwise conducted under our IND, including our current clinical trials evaluating RMC-4630. Once we have completed all clinical trials for a product candidate that are assigned to us under a development plan, all regulatory approvals for such product candidate are automatically assigned to Sanofi. Unless otherwise delegated to us by the joint commercialization committee, Sanofi also has the sole right and responsibility for all aspects of the commercialization of SHP2 inhibitors in the world for any and all uses, at its expense, subject to our right to elect to co-promote SHP2 inhibitors in the United States. Sanofi is obligated to use commercially reasonable efforts to seek marketing approval for at least one SHP2 inhibitor product candidate in certain major market countries. Sanofi agrees to provide us, and we agree to provide Sanofi, with research, development and commercialization updates through the joint committees.

During the term of the Sanofi Agreement, we may not, alone or with any affiliate or third party, conduct certain research activities with respect to, or develop or commercialize, any product that contains a SHP2 inhibitor outside of the Sanofi Agreement.

Pursuant to the Sanofi Agreement, we received an upfront payment of \$50 million from Sanofi in July 2018. Upon the achievement of specified development and regulatory milestones, Sanofi will be obligated to pay us up to \$520 million in the aggregate, including up to \$235 million upon the achievement of specified development milestones and up to \$285 million upon achievement of certain marketing approval milestones. In the United States, we will share equally with Sanofi the profits and losses applicable to commercialization of SHP2 inhibitor products, pursuant to a profit/loss share agreement that the parties will negotiate based on key terms agreed in the Sanofi Agreement. On a product-by-product basis, Sanofi will also be required to pay us tiered royalties on annual net sales of each product outside the United States ranging from high single digit to mid-teen percentages. The royalty payments are subject to reduction under specified conditions set forth in the Sanofi Agreement. Subject to certain exceptions, the royalties are payable on a product-by-product and

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country-by-country basis until the latest of the expiration of all valid claims covering such product in such country contained in the patents licensed to Sanofi under the Sanofi Agreement and the expiration of regulatory exclusivity for such product in such country.

Sanofi has the sole and exclusive right to file, prosecute and maintain any patents licensed to it pursuant to the Sanofi Agreement, as well as to enforce infringement of or defend claims against such patents that relate to SHP2 inhibitor products.

Unless terminated earlier, the Sanofi Agreement will continue in effect until the later of the expiration of all of Sanofi's milestone and royalty payment obligations and the expiration of the profit/loss share agreement. Upon expiration of the Sanofi Agreement, the licenses granted to Sanofi thereunder shall become fully paid-up, royalty-free, perpetual and irrevocable. Sanofi may terminate the Sanofi Agreement in its entirety or on a country-by-country or product-by-product basis for any reason or for significant safety concerns, upon prior notice to us within certain specified time periods. Sanofi may terminate the Sanofi Agreement in its entirety upon our change of control, with prior notice. Either party may terminate the Sanofi Agreement if an undisputed material breach by the other party is not cured within a defined period of time, or immediately upon notice for insolvency-related events of the other party. We may terminate the Sanofi Agreement after a certain number of years if Sanofi develops a competing program without commencing a registrational clinical trial for a SHP2 inhibitor product candidate, and subject to certain other conditions. We may also terminate the Sanofi Agreement at any time, if Sanofi ceases certain critical activities for SHP2 inhibitor product candidates for more than a specified period of time, provided that such cessations of critical activity were not a result of certain specified factors, and subject to certain other conditions. Upon any termination of the Sanofi Agreement with respect to any product or country, all licenses to Sanofi with respect to such product or country shall automatically terminate and all rights generally revert back to us. If the Sanofi Agreement is terminated, in its entirety or with respect to a product, other than by us for Sanofi's material breach or insolvency, we may be required to pay Sanofi royalties on worldwide net sales of reverted products up to mid-single digit percentages based on the development and regulatory status of such reverted products, in each case subject to reductions in accordance with the terms of the Sanofi Agreement.

Acquisition of Warp Drive

In October 2018, we entered into an Agreement and Plan of Merger pursuant to which we acquired all outstanding shares of Warp Drive. In connection with the acquisition, we issued 6,797,915 shares of our Series B preferred stock and provided \$0.9 million in other consideration, for total consideration valued at \$69.0 million. The Agreement and Plan of Merger contained representations, warranties and covenants by, among and for the benefit of the parties, as well as mutual indemnification obligations.

Manufacturing

We rely on and will continue to rely on our contract manufacturing organizations, or CMOs, for both drug substance and drug product. Currently, all of our manufacturing is outsourced to well-established third-party manufacturers. We have entered into contracts with CMOs for production of RMC-4630 and RMC-5552 drug substance and drug product for our clinical trials and IND-enabling development studies, respectively, and plan to enter into additional contracts with these or other manufacturers for additional supply.

Our outsourced approach to manufacturing relies on CMOs to first develop manufacturing processes that are compliant with current Good Manufacturing Practice, or cGMP, then produce material for preclinical and clinical studies. Our agreements with CMOs may obligate them to develop and qualify upstream and downstream processes, develop drug product process, validate (and in some cases develop) suitable analytical methods for

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test and release as well as stability testing, produce drug substance for preclinical testing, produce cGMP-compliant drug substance, or produce cGMP-compliant drug product. We, and Sanofi, conduct audits of CMOs prior to initiation of activities under these agreements and monitor operations to ensure compliance with the mutually agreed process descriptions and to cGMP regulations.

Competition

The biotechnology and pharmaceutical industries, and the oncology sector, are characterized by rapid evolution of technologies, fierce competition and strong defense of intellectual property rights. While we believe that our discovery programs, technology, knowledge, experience, and scientific resources provide us with competitive advantages, we face competition from major pharmaceutical and biotechnology companies, academic institutions, governmental agencies and public and private research institutions, among others.

Any product candidates that we successfully develop and commercialize will compete with currently approved therapies and new therapies that may become available in the future. Key product features that would affect our ability to effectively compete with other therapeutics include the efficacy, safety and convenience of our products and the ease of use and effectiveness of any complementary diagnostics and/or companion diagnostics.

There is a large number of companies developing or marketing treatments for cancer, including many major pharmaceutical and biotechnology companies. These treatments consist of small molecule drug products, biologics, cell-based therapies and traditional chemotherapy. There are also several programs in development targeting SHP2, including those clinical programs run by Novartis AG, Jacobio Pharmaceuticals Co. Ltd., and Relay Therapeutics, Inc. There are several RAS pathway mutations programs, including those directed at KRASG12C(OFF) and KRASG12D(OFF) mutations, including clinical programs directed at KRASG12C(OFF) being conducted by Amgen Inc., Mirati Therapeutics, Inc., Johnson & Johnson, AstraZeneca plc and Eli Lilly & Co. Other clinical programs directed at mutant RAS are being conducted by Merck & Co./Moderna Therapeutics, Boehringer Ingelheim and Gilead Sciences, Inc. Smaller and other early stage companies may also prove to be significant competitors. In addition, academic research departments and public and private research institutions may be conducting research on compounds that could prove to be competitive.

The availability of coverage and reimbursement from government and other third-party payors will also significantly affect the pricing and competitiveness of our products. Our competitors also may obtain U.S. Food and Drug Administration, or the FDA, or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market.

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

Intellectual property

Our success depends in part on our ability and the ability of our collaborators to obtain and maintain proprietary protection for our technology, programs, and know-how related to our business, defend and

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enforce our intellectual property rights, in particular, our patent rights, preserve the confidentiality of our trade secrets, and operate without infringing valid and enforceable intellectual property rights of others. We endeavor to establish, maintain and enforce intellectual property rights that protect our business interests.

The term of individual patents depends upon the legal term of patents in the countries in which they are obtained. In most countries in which we file, including the United States, the patent term is generally 20 years from the earliest date of filing a non-provisional patent application, assuming the patent has not been terminally disclaimed over a commonly-owned patent or a patent naming a common inventor, or over a patent not commonly owned but that was disqualified as prior art as the result of activities undertaken within the scope of a joint research agreement. In the United States, the term of a patent may also be eligible for patent term adjustment for delays within the United States Patent and Trademark Office, or USPTO. In addition, for patents that cover an FDA-approved drug, the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, may permit a patent term extension of up to five years beyond the expiration of the patent. While the length of such patent term extension is related to the length of time the drug is under regulatory review, patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent per approved drug may be extended and only those claims covering the approved drug product, a method for using it or a method for manufacturing it may be extended. Similar provisions are available in Europe and certain other foreign jurisdictions to extend the term of a patent that covers an approved drug. In the future, if and when our products receive FDA approval, we expect to apply for patent term extensions on patents covering those products. We plan to seek any available patent term extension to any issued patents we may be granted in any jurisdiction where such extensions are available; however, there is no guarantee that the applicable authorities, including the FDA in the United States, will agree with our assessment of whether such extensions should be granted, and if granted, the length of such extensions.

We also rely on trade secrets, know-how, and confidential information relating to our programs to develop and maintain our proprietary position, and seek to protect and maintain the confidentiality of such items to protect aspects of our business that are not amenable to, or that we do not presently consider appropriate for, patent protection. Our trade secrets include, for example, certain program specific syntheses, manufacturing schema, formulations, biomarkers, patient selection strategies, and certain aspects of our proprietary tri-complex technology platform. It is our policy to require our employees, consultants, contractors, outside scientific collaborators, sponsored researchers and other advisors to execute confidentiality agreements prior to the commencement of employment or consulting relationships with us, and for employees, contractors and consultants to enter into invention assignment agreements with us. These agreements generally provide that all confidential information developed or made known to the individual during the course of the individual's relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. Where applicable, the agreements provide that all inventions to which the individual contributed as an inventor shall be assigned to us, and as such, will become our property. There can be no assurance, however, that these agreements will be self-executing or otherwise provide meaningful protection or adequate remedies for our trade secrets or other proprietary information, including in the event of unauthorized use or disclosure of such information. We also seek to preserve the integrity and confidentiality of our trade secrets and confidential information by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in the measures we take to protect and preserve our trade secrets, such measures can be breached, and we may not have adequate remedies for any such breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. For more information regarding the risks related to intellectual property, please see "Risk factors—Risks related to intellectual property."

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Our program-specific patent portfolio

Our patent portfolio is directed to small molecules, platform methodologies, and related technology. We seek patent protection for product candidates, development programs, and related alternatives by filing and prosecuting patent applications in the United States and other countries, as appropriate.

We own and co-own patent applications related to our SHP2 development program. As of March 31, 2020, our patent portfolio related to this program consists of ownership or co-ownership rights to one issued U.S. patent, five pending U.S. non-provisional patent applications, five pending applications under the Patent Cooperation Treaty, or PCT, and approximately 92 pending patent applications in other jurisdictions, including without limitation major markets such as Brazil, Canada, China, Europe, Japan, Mexico and South Korea, within eight total patent families that include patent applications covering compositions of matter or methods of using our clinical candidate, RMC-4630, alone or in combination with certain other therapeutic agents. The single co-owned patent family is co-owned with The University of California, San Francisco, or UCSF. Any patents issuing from these patent applications would have nominal expiration dates ranging from 2037 to 2039, without accounting for any applicable patent term adjustments or extensions. All but the single UCSF co-owned family is exclusively licensed to our SHP2 collaborator, Sanofi, under the Sanofi Agreement.

We own or exclusively license patents and patent applications related to our 4EBP1/mTORC1 development program. As of March 31, 2020, our patent portfolio related to this program consists of ownership or the exclusive license of rights to one issued U.S. patent, four pending U.S. non-provisional patent applications, two pending PCT applications and 18 pending patent applications in other jurisdictions, including without limitation major markets such as Canada, China, Europe, Japan and Mexico, within four total patent families that include filings covering compositions of matter or methods of using our development candidate, RMC-5552, alone or in combination with certain other therapeutic agents. The single exclusively licensed patent family is licensed from UCSF. The issued patent has, and any patents issuing from these patent applications would have, nominal expiration dates ranging from 2035 to 2039, without accounting for any applicable patent term adjustments or extensions.

We own patents and patent applications related to our RAS tri-complex inhibitors and related platform technology. As of March 31, 2020, our patent portfolio related to this program consists of ownership rights to five issued U.S. patents, six pending U.S. non-provisional patent applications, one pending PCT applications and approximately twenty-seven pending patent applications in other jurisdictions, including without limitation major markets such as Canada, Europe and Japan, within six total patent families that include filings covering compositions of matter, methods of using those compositions alone or in combination with certain other therapeutic agents, or aspects pertaining to our tri-complex approach to RAS inhibition. The issued patents have, and any patents issuing from these patent applications would have, nominal expiration dates ranging from 2031 to 2040, without accounting for any applicable patent term adjustments or extensions.

Government regulation

The FDA and other regulatory authorities at federal, state, and local levels, as well as in foreign countries, extensively regulate, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, marketing and promotion, distribution, post-approval monitoring and reporting, sampling, and import and export of products, such as those we are developing. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources.

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U.S. drug regulation

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations. FDA approval is required before any new unapproved drug can be marketed in the United States. Drugs are also subject to other federal, state and local statutes and regulations. Failure to comply with applicable FDA or other requirements may subject a company to a variety of administrative or judicial sanctions, such as FDA clinical holds, refusal to approve pending applications, withdrawal of an approval, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties and criminal prosecution.

The process required by the FDA before product candidates may be marketed in the United States generally involves the following:

- completion of preclinical laboratory tests and animal studies, where all supporting safety and toxicity studies are performed in accordance with the FDA's Good Laboratory Practice, or GLP, regulations;
- manufacture of clinical drug supply in accordance with FDA's current Good Manufacturing Practice, or cGMP, regulations, when required;
- submission to the FDA of an investigational new drug application, or IND, which must become effective before human clinical studies may begin and must be updated annually or when significant changes are made;
- approval by an independent institutional review board, or IRB, representing each clinical site before a clinical study may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practice, or GCP, regulations to establish the safety and efficacy of the product candidate for each proposed indication;
- preparation of and submission to the FDA of an NDA;
- a determination by the FDA within 60 days of its receipt of an NDA to file the application for review;
- satisfactory completion of an FDA advisory committee review, if applicable;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility(ies) where the product is manufactured to assess compliance with current good manufacturing practice, or cGMP, regulations, and of selected clinical investigation sites to assess compliance with GCP; and
- FDA review and approval of an NDA to permit commercial marketing of the product for its particular labeled uses in the United States.

Preclinical and clinical studies

The preclinical and clinical testing and approval process can take many years and the actual time required to obtain approval, if any, may vary substantially based upon the type, complexity and novelty of the product or condition being treated.

Preclinical tests include laboratory (in vitro) evaluation of product chemistry, formulation and toxicity, as well as animal (in vivo) studies to assess the characteristics and potential safety and efficacy of the product. The conduct of preclinical tests that provide safety and toxicological information must comply with federal regulations and requirements, including GLP. The results of preclinical testing are submitted to the FDA as part of an IND along with other information, including information about product chemistry, manufacturing and

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controls (CMC) and any available human data or literature to support use of the product in humans. Long-term preclinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue after the IND is submitted.

The central focus of an IND submission is on the general investigational plan and the protocol(s) for human studies. An IND must become effective before human clinical trials may begin. An IND will automatically become effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to the proposed clinical studies. In such a case, the IND may be placed on clinical hold and the IND sponsor and the FDA must resolve any outstanding concerns or questions before clinical studies can begin.

For each successive clinical trial conducted with the investigational drug, a separate, new protocol submission to an existing IND must be made, along with any subsequent changes to the investigational plan. Sponsors are also subject to ongoing reporting requirements, including submission of IND safety reports for any serious adverse experiences associated with use of the investigational drug or findings from preclinical studies suggesting a significant risk for human subjects, as well as IND annual reports on the progress of the investigations conducted under the IND.

Clinical studies involve the administration of the investigational new drug to human subjects under the supervision of qualified investigators in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for participation in each clinical study. Clinical studies are conducted under protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety and the efficacy criteria to be evaluated. A protocol for each clinical study and any subsequent protocol amendments must be submitted to the FDA as part of the IND. Additionally, approval must also be obtained from each clinical study site's IRB before a study may be initiated at the site, and the IRB must monitor the study until completed. Sponsors of clinical trials generally must register and report ongoing clinical studies and clinical study results to public registries, including the website maintained by the U.S. National Institutes of Health, ClinicalTrials.gov.

For purposes of NDA approval, human clinical trials are typically divided into three or four phases. Although the phases are usually conducted sequentially, they may overlap or be combined.

- Phase 1. The drug is initially introduced into healthy human subjects or into patients with the target disease or condition. These studies are designed to evaluate the safety, dosage tolerance, metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and if possible, to gain early evidence on effectiveness.
- Phase 2. The drug is administered to a limited patient population to evaluate tolerance and optimal dose, identify possible adverse side effects and safety risks, and preliminarily evaluate efficacy. Multiple Phase 2 trials may be conducted to obtain additional data prior to beginning Phase 3 trials.
- Phase 3. The drug is administered to an expanded patient population, generally at geographically dispersed clinical study sites to generate enough data to statistically evaluate dosage, clinical effectiveness and safety, to establish the overall benefit-risk relationship of the investigational product and to provide an adequate basis for product approval.
- Phase 4. In some cases, the FDA may condition approval of an NDA for a product candidate on the sponsor's agreement to conduct additional clinical studies after approval. In other cases, a sponsor may voluntarily conduct additional clinical studies after approval to gain more information about the drug. Such post-approval studies are typically referred to as Phase 4 clinical studies.

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The FDA, the IRB or the clinical study sponsor may suspend or terminate a clinical study at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. The sponsor may also suspend or terminate a clinical study based on evolving business objectives and/or competitive climate.

Concurrent with clinical trials, companies may complete additional in vivo studies and develop additional information about the characteristics of the product candidate. Companies must also finalize a process for manufacturing the product in commercially applicable quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product and, among other things, must use validated methods for testing the product against specifications to confirm its identity, strength, quality and purity. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product does not undergo unacceptable deterioration over its shelf life.

Submission of an NDA to the FDA

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, the results of product development and testing are submitted to the FDA in the form of an NDA requesting approval to market the product for one or more indications. The submission of an NDA requires payment of a substantial application user fee to the FDA, unless a waiver or exemption applies.

An NDA must include all relevant data available from pertinent preclinical and clinical studies, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls and proposed labeling, among other things. Data can come from company-sponsored clinical studies intended to test the safety and effectiveness of a use of a product, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and effectiveness of the investigational product to the satisfaction of the FDA.

The FDA has 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an application for filing. In this event, the application must be resubmitted with the additional information and is subject to payment of additional user fees. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. Under applicable Prescription Drug User Fee Act, or PDUFA, performance goals, the FDA endeavors to review applications subject to standard review within ten to twelve months, and to review applications subject to priority review within six to eight months, depending on whether the drug is a new molecular entity.

The FDA may refer applications for novel drug products or drug products which present difficult questions of safety or efficacy to an advisory committee for review, evaluation and recommendation as to whether the application should be approved and under what conditions.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, the FDA will typically inspect one or more clinical sites to assure that relevant study data was obtained in compliance with GCP requirements.

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After the FDA evaluates the NDA and conducts inspections of manufacturing facilities, it may issue an approval letter or a complete response letter. A complete response letter indicates that the review cycle of the application is complete and the application is not ready for approval. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. Even with submission of this additional information, the FDA may ultimately decide that an application does not satisfy the regulatory criteria for approval. If, or when, the deficiencies have been addressed to the FDA's satisfaction in a resubmission of the application, the FDA will issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications.

As a condition of NDA approval, the FDA may require a Risk Evaluation and Mitigation Strategy, or REMS, program to help ensure that the benefits of the drug outweigh its risks. If the FDA determines a REMS program is necessary during review of the application, the drug sponsor must agree to the REMS plan at the time of approval. A REMS program may be required to include various elements, such as a medication guide or patient package insert, a communication plan to educate healthcare providers of the drug's risks, or other elements to assure safe use, such as limitations on who may prescribe or dispense the drug, dispensing only under certain circumstances, special monitoring and the use of patient registries. In addition, all REMS programs must include a timetable to periodically assess the strategy following implementation.

Further, product approval may require substantial post-approval testing and surveillance to monitor the drug's safety and efficacy, and the FDA has the authority to prevent or limit further marketing of a product based on the results of these post-marketing programs. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing. Moreover, changes to the conditions established in an approved application, including changes in indications, labeling or manufacturing processes or facilities may require submission and FDA approval of a new NDA or NDA supplement before the changes can be implemented. An NDA supplement for a new indication typically requires clinical data similar to that supporting the original approval, and the FDA uses similar procedures in reviewing supplements as it does in reviewing original applications.

Expedited development and review programs

The FDA offers a number of expedited development and review programs for qualifying product candidates, one or more of which may be available for our current or future products.

New drug products are eligible for fast track designation if they are intended to treat a serious or life-threatening disease or condition and demonstrate the potential to address unmet medical needs for the disease or condition. Fast track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a fast track product has opportunities for frequent interactions with the review team during product development and, once an NDA is submitted, the product may be eligible for priority review. A fast track product may also be eligible for rolling review, where the FDA may consider for review sections of the NDA on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the NDA.

A product intended to treat a serious or life-threatening disease or condition may also be eligible for breakthrough therapy designation to expedite its development and review. A product can receive breakthrough therapy designation if preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial

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treatment effects observed early in clinical development. The designation includes all of the fast track program features, as well as more intensive FDA interaction and guidance beginning as early as Phase 1 and an organizational commitment to expedite the development and review of the product, including involvement of senior managers.

After an NDA is submitted for a product, including a product with a fast track designation and/or breakthrough therapy designation, the NDA may be eligible for priority review. A product is eligible for priority review if it has the potential to provide a significant improvement in the treatment, diagnosis or prevention of a serious disease or condition compared to marketed products. Depending on whether a drug contains a new molecular entity, priority review designation means the FDA's goal is to take an action on the marketing application within six to eight months of the 60-day filing date, compared with ten to twelve months under standard review.

Additionally, products studied for their safety and effectiveness in treating serious or life-threatening diseases or conditions may receive accelerated approval upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. As a condition of accelerated approval, the FDA will generally require the sponsor to perform adequate and well-controlled post-marketing clinical studies to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product.

Orphan drug designation

We intend to pursue orphan drug designation with respect to oncology indications, as appropriate, with the potential to obtain orphan drug exclusivity for our products, if approved.

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug intended to treat a rare disease or condition, which is a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for this type of disease or condition will be recovered from sales in the United States for that drug. Orphan drug designation must be requested before submitting an NDA. After the FDA grants orphan drug designation, the generic identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. The orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review or approval process.

If a product that has orphan drug designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan drug exclusive approval (or exclusivity), which means that the FDA may not approve any other applications, including a full NDA, to market the same drug for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity. Orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition. Among the other benefits of orphan drug designation are tax credits for certain research and a waiver of the application user fee.

A designated orphan drug may not receive orphan drug exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation. In addition, exclusive marketing rights in the United States may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition.

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Pediatric information and pediatric exclusivity

Under the Pediatric Research Equity Act, or PREA, certain NDAs and certain supplements to an NDA must contain data to assess the safety and efficacy of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of pediatric data or full or partial waivers. The Food and Drug Administration Safety and Innovation Act, or FDASIA, amended the FDCA to require that a sponsor who is planning to submit a marketing application for a drug that includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration submit an initial Pediatric Study Plan, or iPSP, within 60 days of an end-of-Phase 2 meeting or, if there is no such meeting, as early as practicable before the initiation of a Phase 3 or Phase 2/3 study. The iPSP must include an outline of the pediatric study or studies that the sponsor plans to conduct, including study objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information. The FDA and the sponsor must reach an agreement on the iPSP. A sponsor can submit amendments to an agreed-upon iPSP at any time if changes to the pediatric plan need to be considered based on data collected from preclinical studies, early phase clinical trials and/or other clinical development programs.

A drug product can also obtain pediatric market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric study in accordance with an FDA-issued "Written Request" for such a study.

Post-approval requirements

Once an NDA is approved, a product will be subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to drug listing and registration, recordkeeping, periodic reporting, product sampling and distribution, adverse event reporting and advertising, marketing and promotion. Drugs may be marketed only for the approved indications and in accordance with the provisions of the approved labeling. While physicians may prescribe for off-label uses, manufacturers may only promote for the approved indications and in accordance with the provisions of the approved label. However, companies may share truthful and not misleading information that is otherwise consistent with a product's FDA approved labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing user fee requirements, under which FDA assesses an annual program fee for each product identified in an approved NDA. In addition, quality-control, drug manufacture, packaging and labeling procedures must continue to conform to cGMPs after approval. Drug manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies. Registration with the FDA subjects entities to periodic unannounced and announced inspections by the FDA and these state agencies, during which the agency inspects manufacturing facilities to assess compliance with cGMPs. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting requirements upon us and any third-party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other aspects of regulatory compliance.

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The FDA may withdraw approval of a product if compliance with regulatory requirements is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical studies to assess new safety risks; or imposition of distribution restrictions or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of a product, complete withdrawal of the product from the market or product recalls;
- fines, warning or untitled letters or holds on post-approval clinical studies;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of existing product approvals;
- product seizure or detention, or refusal of the FDA to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA may also require post-approval studies and clinical trials if the FDA finds that scientific data, including information regarding related drugs, deem it appropriate. The purpose of such studies would be to assess a known serious risk or signals of serious risk related to the drug or to identify an unexpected serious risk when available data indicate the potential for a serious risk. The FDA may also require a labeling change if it becomes aware of new safety information that it believes should be included in the labeling of a drug.

International regulation

In addition to regulations in the United States, we could become subject to a variety of foreign regulations regarding development, approval, commercial sales and distribution of our products if we seek to market our product candidates in other jurisdictions. Whether or not we obtain FDA approval for a product, we must obtain the necessary approvals by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the product in those countries. The approval process varies from country to country and can involve additional product testing and additional review periods, and the time may be longer or shorter than that required to obtain FDA approval. The requirements governing, among other things, the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from country to country. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others. If we fail to comply with applicable foreign regulatory requirements, we may be subject to fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Other healthcare laws

Pharmaceutical companies are subject to additional healthcare regulation and enforcement by the federal government and by authorities in the states and foreign jurisdictions in which they conduct their business. Such laws include, without limitation, U.S. federal and state anti-kickback, fraud and abuse, false claims, consumer fraud, pricing reporting, data privacy and security, and transparency laws and regulations as well as similar foreign laws in jurisdictions outside the U.S.

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For example, the federal Anti-Kickback Statute prohibits, among other things, individuals or entities from knowingly and willfully offering, paying, soliciting or receiving remuneration, directly or indirectly, overtly or covertly, in cash or in kind to induce or in return for purchasing, leasing, ordering or arranging for or recommending the purchase, lease or order of any item or service reimbursable under Medicare, Medicaid or other federal healthcare programs. A person or entity does not need to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act and the civil monetary penalties statute. The federal civil and criminal false claims laws, including the civil False Claims Act, prohibit, among other things, any individual or entity from knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created additional federal civil and criminal statutes that prohibit, among other things, knowingly and willfully executing a scheme to defraud any healthcare benefit program. Similar to the U.S. federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the healthcare fraud statute implemented under HIPAA or specific intent to violate it in order to have committed a violation. The federal Physician Payments Sunshine Act requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to CMS information related to payments or other transfers of value made to physicians (as defined by statute) and teaching hospitals, and applicable manufacturers and applicable group purchasing organizations to report annually to CMS ownership and investment interests held by physicians and their immediate family members. Beginning in 2022, applicable manufacturers also will be required to report such information regarding payments and transfers of value provided, as well as ownership and investment interests held, during the previous year to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists and certified nurse midwives.

Similar state and local laws and regulations may also restrict business practices in the pharmaceutical industry, such as state anti-kickback and false claims laws, which may apply to business practices, including but not limited to, research, distribution, sales and marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, or by patients themselves; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws and regulations that require drug manufacturers to file reports relating to pricing and marketing information or which require tracking gifts and other remuneration and items of value provided to physicians, other healthcare providers and entities; and state and local laws that require the registration of pharmaceutical sales representatives. Violation of any of such laws or any other governmental regulations that apply may result in penalties, including, without limitation, civil and criminal penalties, damages, fines, additional reporting obligation, the curtailment or restructuring of operations, exclusion from participation in governmental healthcare programs and individual imprisonment.

Data privacy and security laws

Pharmaceutical companies may be subject to U.S. federal and state health information privacy, security and data breach notification laws, which may govern the collection, use, disclosure and protection of health-related and other personal information. State laws may be more stringent, broader in scope or offer greater individual rights with respect to protected health information, or PHI, than HIPAA and state laws may differ from each other, which may complicate compliance efforts. Entities that are found to be in violation of HIPAA as the result

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of a breach of unsecured PHI, a complaint about privacy practices or an audit by the Department of Health and Human Services, or HHS, may be subject to significant civil, criminal and administrative fines and penalties and/or additional reporting and oversight obligations if required to enter into a resolution agreement and corrective action plan with HHS to settle allegations of HIPAA non-compliance. In addition, California enacted the California Consumer Privacy Act, or CCPA, which creates individual privacy rights for California consumers and increases the privacy and security obligations of entities handling certain personal data. The CCPA went into effect on January 1, 2020, and the California Attorney General may bring enforcement actions for violations beginning July 1, 2020. The CCPA has been amended from time to time, and it remains unclear what, if any, further modifications will be made to this legislation or how it will be interpreted.

European Union member states, the United Kingdom, Switzerland and other jurisdictions have also adopted data protection laws and regulations, which impose significant compliance obligations. In the European Economic Area, or EEA, and the United Kingdom, the collection and use of personal data, including clinical trial data, is governed by the provisions of the General Data Protection Regulation, or GDPR. The GDPR became effective on May 25, 2018, repealing its predecessor directive and increasing responsibility and liability of pharmaceutical companies in relation to the processing of personal data of EU data subjects. The GDPR, together with national legislation, regulations and guidelines of the EU member states and the United Kingdom governing the processing of personal data, impose strict obligations and restrictions on the ability to collect, analyze, store, transfer and otherwise process personal data, including health data from clinical trials and adverse event reporting. In particular, the GDPR includes obligations and restrictions concerning the consent of the individuals to whom the personal data relates, the information provided to such individuals, the transfer of personal data out of the EEA or the United Kingdom, security breach notifications, security and confidentiality of the personal data and imposition of substantial potential fines for breaches of the data protection obligations. European data protection authorities may interpret the GDPR and national laws differently and impose additional requirements, which add to the complexity of processing personal data in or from the EEA or United Kingdom. Guidance on implementation and compliance practices are often updated or otherwise revised.

Coverage and reimbursement

Sales of any pharmaceutical product depend, in part, on the extent to which such product will be covered by third-party payors, such as federal, state and foreign government healthcare programs, commercial insurance and managed healthcare organizations, and the level of reimbursement for such product by third-party payors. Significant uncertainty exists as to the coverage and reimbursement status of any newly approved product. Decisions regarding the extent of coverage and amount of reimbursement to be provided are made on a plan-by-plan basis. One third-party payor's decision to cover a particular product does not ensure that other payors will also provide coverage for the product. As a result, the coverage determination process can require manufacturers to provide scientific and clinical support for the use of a product to each payor separately and can be a time-consuming process, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

In addition, third-party payors are increasingly reducing reimbursements for pharmaceutical products and services. The U.S. government and state legislatures have continued implementing cost-containment programs, including price controls, restrictions on coverage and reimbursement and requirements for substitution of generic products. Third-party payors are more and more challenging the prices charged, examining the medical necessity and reviewing the cost effectiveness of pharmaceutical products, in addition to questioning their safety and efficacy. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit sales of any product.

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Decreases in third-party reimbursement for any product or a decision by a third-party payor not to cover a product could reduce physician usage and patient demand for the product.

In international markets, reimbursement and healthcare payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. For example, the European Union provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. Pharmaceutical products may face competition from lower-priced products in foreign countries that have placed price controls on pharmaceutical products and may also compete with imported foreign products. Furthermore, there is no assurance that a product will be considered medically reasonable and necessary for a specific indication, will be considered cost-effective by third-party payors, that an adequate level of reimbursement will be established even if coverage is available or that the third-party payors' reimbursement policies will not adversely affect the ability for manufacturers to sell products profitably.

Healthcare reform

In the United States and certain foreign jurisdictions, there have been, and we expect there will continue to be, a number of legislative and regulatory changes to the healthcare system. In March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the ACA, was signed into law, which substantially changed the way healthcare is financed by both governmental and private insurers in the United States. The ACA contains a number of provisions, including those governing enrollment in federal healthcare programs, reimbursement adjustments and fraud and abuse changes. Additionally, the ACA increased the minimum level of Medicaid rebates payable by manufacturers of brand name drugs from 15.1% to 23.1%; required collection of rebates for drugs paid by Medicaid managed care organizations; imposed a non-deductible annual fee on pharmaceutical manufacturers or importers who sell certain "branded prescription drugs" to specified federal government programs; expanded eligibility criteria for Medicaid programs; created a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and established a Center for Medicare Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

Since its enactment, there have been judicial and Congressional challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. For example, in 2017, Congress enacted the Tax Cuts and Jobs Act, or the TCJA, which eliminated the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." On December 14, 2018, a U.S. District Court Judge in the Northern District of Texas, or the Texas District Court Judge, ruled that the individual mandate is a critical and inseparable feature of the ACA, and therefore, because it was repealed as part of the TJCA, the remaining provisions of the ACA are invalid as well. On December 18, 2019, the U.S. Court of Appeals for the 5th Circuit affirmed the District Court's decision that the individual mandate was unconstitutional but remanded the case back to the District Court to determine whether the remaining provisions of the ACA are invalid as well. On March 2, 2020, the United States Supreme Court granted the petitions for writs of certiorari to review this case, although it is unclear how and when the Supreme Court will rule. It is also unclear how other efforts to challenge, repeal or replace the ACA will impact the ACA.

Other legislative changes have been proposed and adopted since the ACA was enacted, including aggregate reductions of Medicare payments to providers of 2% per fiscal year and reduced payments to several types of

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Medicare providers, which will remain in effect through 2029 absent additional congressional action. The Coronavirus Aid, Relief, and Economic Security Act, or CARES Act, suspended these Medicare sequester reductions from May 1, 2020 through December 31, 2020 due to the COVID-19 pandemic, and extended the sequester by one year, through 2030. Moreover, there has recently been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed and enacted legislation designed, among other things, to bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs and reform government program reimbursement methodologies for pharmaceutical products. Individual states in the United States have also become increasingly active in implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures and, in some cases, mechanisms to encourage importation from other countries and bulk purchasing. Furthermore, there has been increased interest by third party payors and governmental authorities in reference pricing systems and publication of discounts and list prices.

Employees

As of March 31, 2020, we had 100 full-time employees. 54 of our employees have M.D. or Ph.D. degrees. Within our workforce, as of March 31, 2020, 84 employees were engaged in research and development and 16 were engaged in business development, finance, legal, and general management and administration. None of our employees are represented by labor unions or covered by collective bargaining agreements. We consider our relationship with our employees to be good.

Facilities

Our corporate headquarters is located in Redwood City, California, where we lease and occupy approximately 61,000 square feet of office and laboratory space. The term of our Redwood City lease expires in December 2030, with an option to extend the term through December 2040. We have subleased approximately 9,700 of our Redwood City lease to AtriCure, Inc. The current term of this sublease expires in December 2020.

We also lease approximately 22,000 square feet of office and laboratory space in Cambridge, Massachusetts. The current term of our Cambridge lease expires in February 2023, with an option to extend the term through February 2028, subject to certain conditions. We have subleased this office and laboratory space to Casma Therapeutics, Inc. The current term of this sublease expires in February 2023.

We believe our existing facilities are sufficient for our needs for the foreseeable future. To meet the future needs of our business, we may lease additional or alternate space, and we believe suitable additional or alternative space will be available in the future on commercially reasonable terms.

Legal proceedings

From time to time, we may become involved in litigation or other legal proceedings. We are not currently a party to any litigation or legal proceedings that, in the opinion of our management, are likely to have a material adverse effect on our business. Regardless of outcome, litigation can have an adverse impact on our business, financial condition, results of operations and prospects because of defense and settlement costs, diversion of management resources and other factors.

Description of capital stock

The following summary describes our capital stock and certain provisions of our amended and restated certificate of incorporation and our amended and restated bylaws, the amended and restated investors' rights agreement to which we and certain of our stockholders are parties and of the Delaware General Corporation Law. 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 amended and restated investors' rights agreement, copies of which are incorporated by reference as exhibits to the registration statement of which this prospectus is part.

General

Our amended and restated certificate of incorporation authorizes 300,000,000 shares of common stock, \$0.0001 par value per share, and 10,000,000 shares of convertible preferred stock, \$0.0001 par value per share. As of March 31, 2020, there were outstanding:

- 5,568,324 shares of our common stock issuable upon exercise of outstanding stock options; and
- 59,003,644 shares of our common stock held by approximately 210 stockholders of record. This number does not include beneficial owners whose shares are held by nominees in street name.

Common stock

Voting rights

Each holder of our common stock is entitled to one vote for each share on all matters submitted to a vote of the stockholders, including the election of directors. Our stockholders do not have cumulative voting rights in the election of directors. Accordingly, holders of a majority of the voting shares are able to elect all of the directors. In addition, the affirmative vote of holders of 66-2/3% of the voting power of all of the then outstanding voting stock is required to take certain actions, including amending certain provisions of our amended and restated certificate of incorporation, such as the provisions relating to amending our amended and restated bylaws, the classified board and director liability.

Dividends

Subject to preferences that may be applicable to any then outstanding preferred stock, holders of our common stock are entitled to receive dividends, if any, as may be declared from time to time by our board of directors out of legally available funds.

Liquidation

In the event of our liquidation, dissolution or winding up, holders of our common stock will be entitled to share ratably in the net assets legally available for distribution to stockholders after the payment of all of our debts and other liabilities and the satisfaction of any liquidation preference granted to the holders of any then outstanding shares of 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

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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 of our outstanding shares of common stock are, and the shares of common stock to be issued in this offering will be, fully paid and nonassessable.

Preferred stock

Our board of directors has the authority, without further action by our stockholders, to issue up to 10,000,000 shares of preferred stock in one or more series and to fix the rights, preferences, privileges and restrictions thereof. These rights, preferences and privileges could include dividend rights, conversion rights, voting rights, terms of redemption, liquidation preferences, sinking fund terms and the number of shares constituting, or the designation of, such series, any or all of which may be greater than the rights of common stock. The issuance of our preferred stock could adversely affect the voting power of holders of common stock and the likelihood that such holders will receive dividend payments and payments upon our liquidation. In addition, the issuance of preferred stock could have the effect of delaying, deferring or preventing a change in control of our company or other corporate action. After the consummation of this offering, no shares of preferred stock will be outstanding, and we have no present plan to issue any shares of preferred stock.

Options

As of March 31, 2020, we had outstanding options to purchase 5,568,324 shares of our common stock, with a per share weighted-average exercise price of \$5.29, under our 2014 Equity Incentive Plan and 2020 Equity Incentive Award Plan.

Registration rights

Under our amended and restated investors' rights agreement, based on the number of shares outstanding as of March 31, 2020, the holders of approximately 39.6 million shares of common stock, or their transferees, have the right to require us to register their shares under the Securities Act so that those shares may be publicly resold, and the holders of approximately 39.6 million shares of common stock, or their transferees, have the right to include their shares in any registration statement we file, in each case as described below.

Form S-1 demand registration rights

The holders of approximately 39.6 million shares of our common stock, or their transferees, are entitled to certain Form S-1 demand registration rights. On or after August 11, 2020, the holders of at least a majority of these shares can request that we register all or a portion of their shares, so long as such holders request that we register at least 40% of the shares entitled to these demand registration rights. These stockholders may make up to two requests for registration on Form S-1.

Form S-3 demand registration rights

The holders of approximately 39.6 million shares of our common stock, or their transferees, are entitled to certain Form S-3 demand registration rights. If we are eligible to use a Form S-3 registration statement, the holders of at least 20% of these shares can request that we register all or a portion of their shares on a Form S-3 registration statement if the anticipated aggregate offering price is at least \$5.0 million, net of certain

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expenses related to the sale of the shares. These stockholders may make unlimited requests for registration on Form S-3, provided that we are not obligated to effect, or take any action to effect, a registration on Form S-3 if we have effected two registrations on Form S-3 pursuant to requests by these stockholders within the 12 month period immediately preceding such request.

Piggyback registration rights

In the event that we determine to register any of our securities under the Securities Act (subject to certain exceptions), either for our own account or for the account of other security holders, the holders of approximately 39.6 million shares of our common stock, or their transferees, are entitled to certain "piggyback" registration rights allowing the holders to include their shares in such registration, subject to certain marketing and other limitations. As a result, whenever we propose to file a registration statement under the Securities Act, other than with respect to certain registrations, including related to the sale of securities to employees pursuant to employee benefit plans, the offer and sale of debt securities, or an SEC Rule 145 transaction, the holders of these shares are entitled to notice of the registration and have the right, subject to limitations that the underwriters may impose on the number of shares included in the registration, to include their shares in the registration. In an underwritten offering, the underwriters have the right, subject to specified conditions, to limit the number of shares such holders may include.

Expenses of registration

We will pay the registration expenses, excluding certain expenses related to the sale of shares, of the holders of the shares registered pursuant to the Form S-1 demand, Form S-3 demand and piggyback registration rights described above, including the reasonable expenses of one counsel for the selling holders not to exceed \$25,000.

Expiration of registration rights

The Form S-1 demand, Form S-3 demand and piggyback registration rights described above will terminate, with respect to any particular stockholder, upon the earlier of (i) five years after the consummation of our IPO, (ii) the date that Rule 144 or another similar exemption under the Securities Act is available to such stockholder for the sale of all of such stockholder's shares without limitation during a three-month period, or (iii) upon the consummation of a merger, consolidation or the sale of substantially all of our assets.

Anti-takeover effects of provisions of our amended and restated certificate of incorporation, our amended and restated bylaws and Delaware law

Some provisions of Delaware law and our amended and restated certificate of incorporation and our amended and restated bylaws contain provisions that could make the following transactions more difficult: acquisition of us by means of a tender offer; acquisition of us by means of a proxy contest or otherwise; or removal of our incumbent officers and directors. It is possible that these provisions could make it more difficult to accomplish or could deter transactions that stockholders may otherwise consider to be in their best interest or in our best interests, including transactions that might result in a premium over the market price for our shares.

These provisions, summarized below, are expected to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to encourage persons seeking to acquire control of us to first negotiate with our board of directors. We believe that the benefits of increased protection of our potential ability to negotiate with the proponent of an unfriendly or unsolicited proposal to acquire or restructure us outweigh the disadvantages of discouraging these proposals because negotiation of these proposals could result in an improvement of their terms.

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Delaware anti-takeover statute

We are subject to Section 203 of the Delaware General Corporation Law, which prohibits persons deemed “interested stockholders” from engaging in a “business combination” with a publicly-held Delaware corporation for three years following the date these persons become interested stockholders unless the business combination is, or the transaction in which the person became an interested stockholder was, approved in a prescribed manner or another prescribed exception applies. Generally, an “interested stockholder” is a person who, together with affiliates and associates, beneficially owns, or within three years prior to the determination of interested stockholder status did own, 15% or more of a corporation’s voting stock. Generally, a “business combination” includes a merger, asset or stock sale, or other transaction resulting in a financial benefit to the interested stockholder. The existence of this provision may have an anti-takeover effect with respect to transactions not approved in advance by the board of directors, such as discouraging takeover attempts that might result in a premium over the market price of our common stock.

Undesignated preferred stock

The ability to issue undesignated preferred stock makes it possible for our board of directors to issue preferred stock with voting or other rights or preferences that could impede the success of any attempt to change control of us. These and other provisions may have the effect of deterring hostile takeovers or delaying changes in control or management of our company.

Special stockholder meetings

Our amended and restated certificate of incorporation and our amended and restated bylaws provide that a special meeting of stockholders may be called only by our board of directors, or by our President or Chief Executive Officer.

Requirements for advance notification of stockholder nominations and proposals

Our amended and restated bylaws establish advance notice procedures with respect to stockholder proposals and the nomination of candidates for election as directors, other than nominations made by or at the direction of the board of directors or a committee of the board of directors.

Elimination of stockholder action by written consent

Our amended and restated certificate of incorporation and our amended and restated bylaws eliminate the right of stockholders to act by written consent without a meeting.

Classified board; election and removal of directors; filling vacancies

Our board of directors is divided into three classes. The directors in each class serves for a three-year term, one class being elected each year by our stockholders, 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. Because our stockholders do not have cumulative voting rights, our stockholders holding a majority of the shares of common stock outstanding will be able to elect all of our directors. Our amended and restated certificate of incorporation provides for the removal of any of our directors only for cause and requires a stockholder vote by the holders of at least a 66-2/3% of the voting power of the then outstanding voting stock. Furthermore, any vacancy on our board of directors, however occurring, including a vacancy resulting from an increase in the size of the board, may only be filled by a

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resolution of the board of directors unless the board of directors determines that such vacancies shall be filled by the stockholders. This system of electing and removing directors and filling vacancies may tend to discourage a third party from making a tender offer or otherwise attempting to obtain control of us, because it generally makes it more difficult for stockholders to replace a majority of the directors.

Choice of forum

Our amended and restated certificate of incorporation to be in effect immediately prior to the consummation of this offering provides that the Court of Chancery of the State of Delaware is the sole and exclusive forum for (i) any state law derivative action or proceeding brought on behalf of us, (ii) any action asserting a claim of breach of a fiduciary duty owed by any of our directors or officers to us or our stockholders, (iii) any action asserting a claim against us arising pursuant to any provision of the Delaware General Corporation Law or our amended and restated certificate of incorporation or amended and restated bylaws or (iv) any action asserting a claim against us governed by the internal affairs doctrine. As a result, any action brought by any of our stockholders with regard to any of these matters will need to be filed in the Court of Chancery of the State of Delaware and cannot be filed in any other jurisdiction; provided that, the exclusive forum provision will not apply to suits brought to enforce any liability or duty created by the Securities Act, the Exchange Act or any other claim for which the federal courts have exclusive jurisdiction; and provided further that, if and only if the Court of Chancery of the State of Delaware dismisses any such action for lack of subject matter jurisdiction, such action may be brought in another state or federal court sitting in the State of Delaware. Nothing in our amended and restated certificate of incorporation or amended and restated bylaws precludes stockholders that assert claims under the Securities Act or the Exchange Act from bringing such claims in state or federal court, subject to applicable law.

This choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or any of our directors, officers, other employees or stockholders, which may discourage lawsuits with respect to such claims, although our stockholders will not be deemed to have waived our compliance with federal securities laws and the rules and regulations thereunder.

Amendment of certificate of incorporation provisions

The amendment of any of the above provisions, except for the provision making it possible for our board of directors to issue undesignated preferred stock, would require approval by a stockholder vote by the holders of at least a 66-2/3% of the voting power of the then outstanding voting stock.

The provisions of the Delaware General Corporation Law, our amended and restated certificate of incorporation and our amended and restated bylaws could have the effect of discouraging others from attempting hostile takeovers and, as a consequence, they may also inhibit temporary fluctuations in the market price of our common stock that often result from actual or rumored hostile takeover attempts. These provisions may also have the effect of preventing changes in our management. It is possible that these provisions could make it more difficult to accomplish transactions that stockholders may otherwise deem to be in their best interests.

Nasdaq Global Select Market listing

Our common stock is listed on the Nasdaq Global Select Market under the symbol "RVMD."

Transfer agent and registrar

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company, LLC. The transfer agent and registrar's address is 6201 15th Avenue, Brooklyn, New York 11219.

Shares eligible for future sale

Future sales of our common stock, including shares issued upon the exercise of outstanding options or warrants, in the public market after this offering, or the perception that those sales may occur, could cause the prevailing market price for our common stock to fall or impair our ability to raise equity capital in the future. As described below, only a limited number of shares of our common stock will be available for sale in the public market after consummation of this offering due to contractual and legal restrictions on resale described below.

Future sales of our common stock in the public market either before (to the extent permitted) or after restrictions lapse, or the perception that those sales may occur, could adversely affect the prevailing market price of our common stock at such time and our ability to raise equity capital at a time and price we deem appropriate.

Based on the number of shares of our common stock outstanding as of March 31, 2020, upon the consummation of this offering and assuming (1) no exercise of the underwriters' option to purchase additional shares of common stock and (2) no exercise of any of our other outstanding options, we will have outstanding an aggregate of _____ shares of common stock.

All of the shares of common stock to be sold in this offering, and any shares sold upon exercise of the underwriters' option to purchase additional shares, will be freely tradable in the public market without restriction or further registration under the Securities Act, unless the shares are held by any of our "affiliates" as such term is defined in Rule 144 of the Securities Act. Certain of the remaining shares of common stock held by existing stockholders immediately prior to the consummation of this offering will be "restricted securities" as such term is defined in Rule 144. These restricted securities were issued and sold by us, or will be issued and sold by us, in private transactions and are eligible for public sale only if registered under the Securities Act or if they qualify for an exemption from registration under the Securities Act, including the exemptions provided by Rule 144 or Rule 701, which rules are summarized below.

Lock-up agreements and market stand-off provisions

In connection with this offering, we, and our directors and officers have agreed, subject to certain exceptions, with the underwriters not to dispose of or hedge any shares of our common stock or securities convertible into or exchangeable for shares of common stock during the period from the date of the lock-up agreement continuing through the date _____ days after the date of this prospectus, except with the prior written consent of _____.

In connection with our initial public offering, we, our directors, our executive officers and substantially all of our other stockholders and option holders agreed, subject to certain exceptions, with the underwriters not to dispose of or hedge any shares of our common stock or securities convertible into or exchangeable for shares of common stock during the period from the date of the lock-up agreement continuing through August 11, 2020, except with the prior written consent of J.P. Morgan Securities LLC.

Subject to certain limitations, certain of our employees, including our executive officers, and/or directors have entered into, and may enter into, written trading plans that are intended to comply with Rule 10b5-1 under the Exchange Act. Sales under these trading plans are not permitted until the expiration of the lock-up agreements relating to our initial public offering described above.

Following the lock-up periods set forth in the market stand-off and lock-up agreements described above, and assuming that _____ does not release any parties from the lock-up agreements, all of the shares of our common stock that are restricted securities or are held by our affiliates as of the date of this prospectus will be eligible for sale in the public market in compliance with Rule 144 under the Securities Act.

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Rule 144

In general, under Rule 144, as currently in effect, once we have been subject to the public company reporting requirements of the Exchange Act, for at least 90 days, a person (or persons whose shares are required to be aggregated) who is not deemed to have been one of our “affiliates” for purposes of Rule 144 at any time during the three months preceding a sale, and who has beneficially owned restricted securities within the meaning of Rule 144 for at least six months, including the holding period of any prior owner other than one of our “affiliates,” is entitled to sell those shares in the public market (subject to the lock-up agreements referred to above, if applicable) without complying with the manner of sale, volume limitations or notice provisions of Rule 144, but subject to compliance with the public information requirements of Rule 144. If such a person has beneficially owned the shares proposed to be sold for at least one year, including the holding period of any prior owner other than “affiliates,” then such person is entitled to sell such shares in the public market without complying with any of the requirements of Rule 144 (subject to the lock-up agreement referred to above, if applicable). In general, under Rule 144, as currently in effect, once we have been subject to the public company reporting requirements of the Exchange Act for at least 90 days, our “affiliates,” as defined in Rule 144, who have beneficially owned the shares proposed to be sold for at least six months are entitled to sell in the public market, upon expiration of any applicable lock-up agreements and within any three-month period, a number of those shares of our common stock that does not exceed the greater of:

- 1% of the number of shares of common stock then outstanding, which will equal approximately _____ shares of common stock immediately after this offering (calculated as of March 31, 2020 on the basis of the assumptions (1)-(2) described above); or
- the average weekly trading volume of our common stock on the Nasdaq Global Select Market during the four calendar weeks preceding the filing of a notice on Form 144 with respect to such sale.

Such sales under Rule 144 by our “affiliates” or persons selling shares on behalf of our “affiliates” are also subject to certain manner of sale provisions, notice requirements and to the availability of current public information about us.

Rule 701

Rule 701 generally provides that a stockholder who purchased shares of our common stock pursuant to a written compensatory benefit plan or contract and who is not deemed to have been one of our affiliates at any time during the preceding 90 days may sell such shares (to the extent such shares are not subject to a lock-up agreement) in reliance upon Rule 144 without complying with the current public information or holding period conditions of Rule 144. Rule 701 also provides that a stockholder who purchased shares of our common stock pursuant to a written compensatory benefit plan or contract and who is deemed to have been one of our affiliates during the preceding 90 days may sell such shares under Rule 144 without complying with the holding period condition of Rule 144 (subject to any applicable lock-up agreement).

Registration rights

The holders of approximately 39.6 million shares of our common stock, or their transferees, will, subject to the lock-up agreements referred to above, be entitled to certain rights with respect to the registration of the offer and sale of those shares under the Securities Act. For a description of these registration rights, see “Description of capital stock—Registration rights.” If the offer and sale of these shares are registered, they will be freely tradable without restriction under the Securities Act.

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Stock plans

We have filed with the SEC a registration statement under the Securities Act covering the shares of common stock reserved for issuance under our 2014 Equity Incentive Plan, our 2020 Incentive Award Plan and our 2020 Employee Stock Purchase Plan. Accordingly, shares registered under such registration statement are available for sale in the open market, subject to Rule 144 volume limitations and the lock-up agreements described above, if applicable.

Material U.S. federal income tax consequences to non-U.S. holders

The following discussion is a summary of the material U.S. federal income tax consequences to Non-U.S. Holders (as defined below) of the purchase, ownership and disposition of our common stock issued pursuant to this offering, but does not purport to be a complete analysis of all potential tax effects. The effects of other U.S. federal tax laws, such as estate and gift tax laws, and any applicable state, local or non-U.S. tax laws are not discussed. This discussion is based on the U.S. Internal Revenue Code of 1986, as amended (“the Code”), Treasury Regulations promulgated thereunder, judicial decisions, and published rulings and administrative pronouncements of the U.S. Internal Revenue Service (“the IRS”), in each case in effect as of the date hereof.

These authorities may change or be subject to differing interpretations. Any such change or differing interpretation may be applied retroactively in a manner that could adversely affect a Non-U.S. Holder. We have not sought and will not seek any rulings from the IRS regarding the matters discussed below. There can be no assurance the IRS or a court will not take a contrary position to that discussed below regarding the tax consequences of the purchase, ownership and disposition of our common stock.

This discussion is limited to Non-U.S. Holders that hold our common stock as a “capital asset” within the meaning of Section 1221 of the Code (generally, property held for investment). This discussion does not address all U.S. federal income tax consequences relevant to a Non-U.S. Holder’s particular circumstances, including the impact of the Medicare contribution tax on net investment income or the alternative minimum tax. In addition, it does not address consequences relevant to Non-U.S. Holders subject to special rules, including, without limitation:

- U.S. expatriates and former citizens or long-term residents of the United States;
- persons holding our common stock as part of a hedge, straddle or other risk reduction strategy or as part of a conversion transaction or other integrated investment;
- banks, insurance companies and other financial institutions;
- brokers, dealers or traders in securities;
- “controlled foreign corporations,” “passive foreign investment companies” and corporations that accumulate earnings to avoid U.S. federal income tax;
- partnerships or other entities or arrangements treated as partnerships for U.S. federal income tax purposes (and investors therein);
- tax-exempt organizations or governmental organizations;
- persons deemed to sell our common stock under the constructive sale provisions of the Code;
- tax-qualified retirement plans; and
- “qualified foreign pension funds” as defined in Section 897(l)(2) of the Code and entities all of the interests of which are held by qualified foreign pension funds.

If an entity treated as a partnership for U.S. federal income tax purposes holds our common stock, the tax treatment of a partner in the partnership will depend on the status of the partner, the activities of the partnership and certain determinations made at the partner level. Accordingly, partnerships holding our common stock and the partners in such partnerships should consult their tax advisors regarding the U.S. federal income tax consequences to them.

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THIS DISCUSSION IS NOT TAX ADVICE. INVESTORS SHOULD CONSULT THEIR TAX ADVISORS WITH RESPECT TO THE APPLICATION OF THE U.S. FEDERAL INCOME TAX LAWS TO THEIR PARTICULAR SITUATIONS AS WELL AS ANY TAX CONSEQUENCES OF THE PURCHASE, OWNERSHIP AND DISPOSITION OF OUR COMMON STOCK ARISING UNDER THE U.S. FEDERAL ESTATE OR GIFT TAX LAWS OR UNDER THE LAWS OF ANY STATE, LOCAL OR NON-U.S. TAXING JURISDICTION OR UNDER ANY APPLICABLE INCOME TAX TREATY.

Definition of non-U.S. holder

For purposes of this discussion, a “Non-U.S. Holder” is any beneficial owner of our common stock that is neither a “U.S. person” nor an entity treated as a partnership for U.S. federal income tax purposes. A U.S. person is any person that, for U.S. federal income tax purposes, is or is treated as any of the following:

- an individual who is a citizen or resident of the United States;
- a corporation created or organized under the laws of the United States, any state thereof or the District of Columbia;
- an estate, the income of which is subject to U.S. federal income tax regardless of its source; or
- a trust that (1) is subject to the primary supervision of a U.S. court and all substantial decisions of which are subject to the control of one or more “United States persons” (within the meaning of Section 7701(a)(30) of the Code), or (2) has a valid election in effect to be treated as a United States person for U.S. federal income tax purposes.

Distributions

As described in the section titled “Dividend policy,” we have never declared or paid cash dividends on our capital stock, and we do not anticipate paying any cash dividends in the foreseeable future. However, if we do make distributions of cash or property 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. Amounts not treated as dividends for U.S. federal income tax purposes will constitute a return of capital and first be applied against and reduce a Non-U.S. Holder’s adjusted tax basis in its common stock, but not below zero. Any excess will be treated as capital gain and will be treated as described below under “—Sale or other taxable disposition.”

Subject to the discussion below regarding effectively connected income, dividends paid to a Non-U.S. Holder will be subject to U.S. federal withholding tax at a rate of 30% of the gross amount of the dividends (or such lower rate specified by an applicable income tax treaty, provided the Non-U.S. Holder furnishes a valid IRS Form W-8BEN or W-8BEN-E (or other applicable documentation) certifying qualification for the lower treaty rate). A Non-U.S. Holder that does not timely furnish the required documentation, but that qualifies for a reduced treaty rate, may obtain a refund of any excess amounts withheld by timely filing an appropriate claim for refund with the IRS. Non-U.S. Holders should consult their tax advisors regarding their entitlement to benefits under any applicable tax treaties.

If dividends paid to a Non-U.S. Holder are effectively connected with the Non-U.S. Holder’s conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, the Non-U.S. Holder maintains a permanent establishment in the United States to which such dividends are attributable), the Non-U.S. Holder will be exempt from the U.S. federal withholding tax described above. To claim the exemption, the Non-U.S. Holder must furnish to the applicable withholding agent a valid IRS Form W-8ECI, certifying that the dividends are effectively connected with the Non-U.S. Holder’s conduct of a trade or business within the United States.

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Any such effectively connected dividends will be subject to U.S. federal income tax on a net income basis at the regular rates. A Non-U.S. Holder that is a corporation also may be subject to a branch profits tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on such effectively connected dividends, as adjusted for certain items. Non-U.S. Holders should consult their tax advisors regarding any applicable tax treaties that may provide for different rules.

Sale or other taxable disposition

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

- the gain is effectively connected with the Non-U.S. Holder's conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, the Non-U.S. Holder maintains a permanent establishment in the United States to which such gain is attributable);
- the Non-U.S. Holder is a nonresident alien individual present in the United States for 183 days or more during the taxable year of the disposition and certain other requirements are met; or
- our common stock constitutes a U.S. real property interest ("USRPI"), by reason of our status as a U.S. real property holding corporation ("USRPHC"), for U.S. federal income tax purposes.

Gain described in the first bullet point above generally will be subject to U.S. federal income tax on a net income basis at the regular rates. A Non-U.S. Holder that is a corporation also may be subject to a branch profits tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on such effectively connected gain, as adjusted for certain items.

Gain described in the second bullet point above will be subject to U.S. federal income tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty), which may be offset by certain U.S. source capital losses of the Non-U.S. Holder (even though the individual is not considered a resident of the United States), provided the Non-U.S. Holder has timely filed U.S. federal income tax returns with respect to such losses.

With respect to the third bullet point above, we believe we currently are not, and do not anticipate becoming, a USRPHC. Because the determination of whether we are a USRPHC depends, however, on the fair market value of our USRPIs relative to the fair market value of our non-U.S. real property interests and our other business assets, there can be no assurance we currently are not a USRPHC or will not become one in the future. 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 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.

Non-U.S. Holders should consult their tax advisors regarding any applicable tax treaties that may provide for different rules.

Information reporting and backup withholding

Payments of dividends on our common stock will not be subject to backup withholding, provided the Non-U.S. Holder certifies its non-U.S. status, such as by furnishing a valid IRS Form W-8BEN, W-8BEN-E or W-8ECI, or otherwise establishes an exemption. However, information returns are required to be filed with the IRS in connection with any distributions on our common stock paid to the Non-U.S. Holder, regardless of whether any tax was actually withheld. In addition, proceeds of the sale or other taxable disposition of our common stock

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within the United States or conducted through certain U.S.-related brokers generally will not be subject to backup withholding or information reporting if the applicable withholding agent receives the certification described above or the Non-U.S. Holder otherwise establishes an exemption. Proceeds of a disposition of our common stock conducted through a non-U.S. office of a non-U.S. broker that does not have certain enumerated relationships with the United States generally will not be subject to backup withholding or information reporting.

Copies of information returns that are filed with the IRS may also be made available under the provisions of an applicable treaty or agreement to the tax authorities of the country in which the Non-U.S. Holder resides or is established.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules may be allowed as a refund or a credit against a Non-U.S. Holder's U.S. federal income tax liability, provided the required information is timely furnished to the IRS.

Additional withholding tax on payments made to foreign accounts

Withholding taxes may be imposed under Sections 1471 to 1474 of the Code (such Sections commonly referred to as the Foreign Account Tax Compliance Act ("FATCA")) on certain types of payments made to non-U.S. financial institutions and certain other non-U.S. entities. Specifically, a 30% withholding tax may be imposed on dividends on, or (subject to the proposed Treasury Regulations discussed below) gross proceeds from the sale or other disposition of, our common stock paid to a "foreign financial institution" or a "non-financial foreign entity" (each as defined in the Code), unless (1) the foreign financial institution undertakes certain diligence and reporting obligations, (2) the non-financial foreign entity either certifies it does not have any "substantial United States owners" (as defined in the Code) or furnishes identifying information regarding each substantial United States owner, or (3) the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from these rules. If the payee is a foreign financial institution and is subject to the diligence and reporting requirements in (1) above, it must enter into an agreement with the U.S. Department of the Treasury requiring, among other things, that it undertake to identify accounts held by certain "specified United States persons" or "United States owned foreign entities" (each as defined in the Code), annually report certain information about such accounts, and withhold 30% on certain payments to non-compliant foreign financial institutions and certain other account holders. Foreign financial institutions located in jurisdictions that have an intergovernmental agreement with the United States governing FATCA may be subject to different rules.

Under the applicable Treasury Regulations and administrative guidance, withholding under FATCA generally applies to payments of dividends on our common stock. While, beginning on January 1, 2019, withholding under FATCA would have applied also to payments of gross proceeds from the sale or other disposition of our common stock, proposed Treasury Regulations eliminate FATCA withholding on payments of gross proceeds entirely. Taxpayers generally may rely on these proposed Treasury Regulations until final Treasury Regulations are issued.

Prospective investors should consult their tax advisors regarding the potential application of withholding under FATCA to their investment in our common stock.

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approximately \$. We have agreed to reimburse the underwriters for expenses of up to \$ relating to the clearance of this offering with the Financial Industry Regulatory Authority.

A prospectus 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.

We have agreed that we will not (i) offer, pledge, announce the intention to sell, 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, lend, or otherwise transfer or dispose of, directly or indirectly, or file with the Securities and Exchange Commission, or SEC, a registration statement under the Securities Act of 1933, relating to, any shares of our common stock or any 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 arrangement 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 for a period of days after the date of this prospectus, other than the shares of our common stock to be sold hereunder and any shares of our common stock issued upon the exercise of options granted under our existing stock-based compensation plans.

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 or entities, with limited exceptions, for a period of days after the date of this prospectus, may not, without the prior written consent of , (1) offer, pledge, announce the intention to sell, 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 and stockholders 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 (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.

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

Our common stock is listed on the Nasdaq Global Select Market under the symbol "RVMD."

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

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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.

Certain of the underwriters and their affiliates have provided in the past to us and our affiliates and may provide from time to time in the future certain commercial banking, financial advisory, investment banking and other services for us and such affiliates in the ordinary course of their business, for which they have received and may continue to receive customary fees and commissions. In addition, from time to time, certain of the underwriters and their affiliates may effect transactions for their own account or the account of customers, and hold on behalf of themselves or their customers, long or short positions in our debt or equity securities or loans, and may do so in the future.

Selling restrictions

General

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 in any jurisdiction where action for that purpose is required. The securities offered by this prospectus may not be offered or sold, directly or indirectly, nor may this prospectus 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 comes are advised to inform themselves about and to observe any restrictions relating to the offering and the distribution of this prospectus. This prospectus does not constitute an offer to sell or a solicitation of an offer to buy any securities offered by this prospectus in any jurisdiction in which such an offer or a solicitation is unlawful.

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Notice to prospective investors in the European Economic Area

In relation to each Member State of the European Economic Area (each a "Member State"), no shares have been offered or will be offered pursuant to the offering to the public in that Member State prior to the publication of a prospectus in relation to the Shares which has been approved by the competent authority in that Member State or, where appropriate, approved in another Member State and notified to the competent authority in that Member State, all in accordance with the Prospectus Regulation), except that offers of shares may be made to the public in that Member State at any time under the following exemptions under the Prospectus Regulation:

- i. to any legal entity which is a qualified investor as defined under the Prospectus Regulation;
- ii. to fewer than 150 natural or legal persons (other than qualified investors as defined in the Prospectus Regulation), subject to obtaining the prior consent of the representatives for any such offer; or
- iii. in any other circumstances falling within Article 1(4) of the Prospectus Regulation;

provided that no such offer of shares shall require the issuer or any underwriter to publish a prospectus pursuant to Article 3 of the Prospectus Regulation or supplement a prospectus pursuant to Article 23 of the Prospectus Regulation 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 Article 2(e) of the Prospectus Regulation. In the case of any shares being offered to a financial intermediary as that term is used in the Prospectus Regulation, 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 Member State to qualified investors as so defined or in circumstances in which the prior consent of the underwriters have been obtained to each such proposed offer or resale.

For the purposes of this provision, the expression an "offer to the public" in relation to any shares in any Member State means the communication in any form and by any means of sufficient information on the terms of the offer and any shares to be offered so as to enable an investor to decide to purchase or subscribe for any shares, and the expression "Prospectus Regulation" means Regulation (EU) 2017/1129.

Notice to prospective investors in the United Kingdom

In addition, in the United Kingdom, this document 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 defined in the Prospectus Regulation) (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 document or use it as basis for taking any action. In the United Kingdom, any investment or investment activity that this document 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

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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 (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 Switzerland

The shares may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange, or SIX, or on any other stock exchange or regulated trading facility in Switzerland. This document does not constitute a prospectus within the meaning of, and has been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this document nor any other offering or marketing material relating to the shares or the offering may be publicly distributed or otherwise made publicly available in Switzerland.

Neither this document nor any other offering or marketing material relating to the offering, the Company, the shares have been or will be filed with or approved by any Swiss regulatory authority. In particular, this document will not be filed with, and the offer of shares will not be supervised by, the Swiss Financial Market Supervisory Authority, or FINMA, and the offer of shares has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes, or CISA. The investor protection afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of shares.

Notice to prospective investors in the Dubai International Financial Centre, or DIFC

This document relates to an Exempt Offer in accordance with the Markets Rules 2012 of the Dubai Financial Services Authority ("DFSA"). This document is intended for distribution only to persons of a type specified in the Markets Rules 2012 of the DFSA. It must not be delivered to, or relied on by, any other person. The DFSA has no responsibility for reviewing or verifying any documents in connection with Exempt Offers. The DFSA has not approved this prospectus supplement nor taken steps to verify the information set forth herein and has no responsibility for this document. The securities to which this document relates may be illiquid and/or subject to restrictions on their resale. Prospective purchasers of the securities offered should conduct their own due diligence on the securities. If you do not understand the contents of this document you should consult an authorized financial advisor.

In relation to its use in the DIFC, this document is strictly private and confidential and is being distributed to a limited number of investors and must not be provided to any person other than the original recipient, and may not be reproduced or used for any other purpose. The interests in the securities may not be offered or sold directly or indirectly to the public in the DIFC.

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Notice to prospective investors in the United Arab Emirates

The shares have not been, and are not being, publicly offered, sold, promoted or advertised in the United Arab Emirates (including the Dubai International Financial Centre) other than in compliance with the laws of the United Arab Emirates (and the Dubai International Financial Centre) governing the issue, offering and sale of securities. Further, this prospectus does not constitute a public offer of securities in the United Arab Emirates (including the Dubai International Financial Centre) and is not intended to be a public offer. This prospectus has not been approved by or filed with the Central Bank of the United Arab Emirates, the Securities and Commodities Authority or the Dubai Financial Services Authority.

Notice to prospective investors in Australia

This prospectus:

- does not constitute a disclosure document or a prospectus under Chapter 6D.2 of the Corporations Act 2001 (Cth) (the “Corporations Act”);
- has not been, and will not be, lodged with the Australian Securities and Investments Commission, or ASIC, as a disclosure document for the purposes of the Corporations Act and does not purport to include the information required of a disclosure document for the purposes of the Corporations Act; and
- may only be provided in Australia to select investors who are able to demonstrate that they fall within one or more of the categories of investors, available under section 708 of the Corporations Act (“Exempt Investors”).

The shares may not be directly or indirectly offered for subscription or purchased or sold, and no invitations to subscribe for or buy the shares may be issued, and no draft or definitive offering memorandum, advertisement or other offering material relating to any shares may be distributed in Australia, except where disclosure to investors is not required under Chapter 6D of the Corporations Act or is otherwise in compliance with all applicable Australian laws and regulations. By submitting an application for the shares, you represent and warrant to us that you are an Exempt Investor.

As any offer of shares under this document will be made without disclosure in Australia under Chapter 6D.2 of the Corporations Act, the offer of those securities for resale in Australia within 12 months may, under section 707 of the Corporations Act, require disclosure to investors under Chapter 6D.2 if none of the exemptions in section 708 applies to that resale. By applying for the shares you undertake to us that you will not, for a period of 12 months from the date of issue of the shares, offer, transfer, assign or otherwise alienate those shares to investors in Australia except in circumstances where disclosure to investors is not required under Chapter 6D.2 of the Corporations Act or where a compliant disclosure document is prepared and lodged with ASIC.

Notice to prospective investors in Japan

The shares have not been and will not be registered pursuant to Article 4, Paragraph 1 of the Financial Instruments and Exchange Act. Accordingly, none of the shares nor any interest therein may be offered or sold, 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 or for the benefit of a resident of Japan, except pursuant to an exemption from the registration requirements of, and otherwise in compliance with, the Financial Instruments and Exchange Act and any other applicable laws, regulations and ministerial guidelines of Japan in effect at the relevant time.

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Notice to prospective investors in Hong Kong

The shares have not been offered or sold and will not be offered or sold in Hong Kong, by means of any document, other than (a) to “professional investors” as defined in the Securities and Futures Ordinance (Cap. 571 of the Laws of Hong Kong), or the SFO, of Hong Kong and any rules made thereunder; or (b) in other circumstances which do not result in the document being a “prospectus” as defined in the Companies (Winding Up and Miscellaneous Provisions) Ordinance (Cap. 32) of Hong Kong), or the CO, or which do not constitute an offer to the public within the meaning of the CO. No advertisement, invitation or document relating to the shares has been or may be issued or has been or may be in the possession of any person for the purposes of issue, 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 of Hong Kong (except if permitted to do so under the securities laws of Hong Kong) other than with respect to shares which are or are intended to be disposed of only to persons outside Hong Kong or only to “professional investors” as defined in the SFO and any rules made thereunder.

Notice to prospective investors in Singapore

Each underwriter has acknowledged that this prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, each underwriter has represented and agreed that it has not offered or sold any shares or caused the shares to be made the subject of an invitation for subscription or purchase and will not offer or sell any shares or cause the shares to be made the subject of an invitation for subscription or purchase, and has not circulated or distributed, nor will it circulate or distribute, this prospectus or any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the shares, whether directly or indirectly, to any person in Singapore other than:

- (a) to an institutional investor (as defined in Section 4A of the Securities and Futures Act (Chapter 289) of Singapore, as modified or amended from time to time, or the SFA) pursuant to Section 274 of the SFA;
- (b) to a relevant person (as defined in Section 275(2) of the SFA) pursuant to Section 275(1) of the SFA, or any person pursuant to Section 275(1A) of the SFA, and in accordance with the conditions specified in Section 275 of the SFA; or
- (c) 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 of the SFA by a relevant person which is:

- (a) a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or
- (b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary of the trust is an individual who is an accredited investor,

securities or securities-based derivatives contracts (each term as defined in Section 2(1) of the SFA) of that corporation or the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferred within six months after that corporation or that trust has acquired the shares pursuant to an offer made under Section 275 of the SFA except:

- (i) to an institutional investor or to a relevant person, or to any person arising from an offer referred to in Section 275(1A) or Section 276(4)(i)(B) of the SFA;
- (ii) where no consideration is or will be given for the transfer;
- (iii) where the transfer is by operation of law;

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- (iv) as specified in Section 276(7) of the SFA; or
- (v) as specified in Regulation 37A of the Securities and Futures (Offers of Investments) (Securities and Securities-based Derivatives Contracts) Regulations 2018.

Singapore SFA Product Classification — In connection with Section 309B of the SFA and the CMP Regulations 2018, unless otherwise specified before an offer of shares, we have determined, and hereby notify all relevant persons (as defined in Section 309A(1) of the SFA), that the shares are “prescribed capital markets products” (as defined in the CMP Regulations 2018) and Excluded Investment Products (as defined in MAS Notice SFA 04-N12: Notice on the Sale of Investment Products and MAS Notice FAA-N16: Notice on Recommendations on Investment Products).

Notice to prospective investors in Bermuda

Shares may be offered or sold in Bermuda only in compliance with the provisions of the Investment Business Act of 2003 of Bermuda which regulates the sale of securities in Bermuda. Additionally, non-Bermudian persons (including companies) may not carry on or engage in any trade or business in Bermuda unless such persons are permitted to do so under applicable Bermuda legislation.

Notice to prospective investors in Saudi Arabia

This document may not be distributed in the Kingdom of Saudi Arabia except to such persons as are permitted under the Offers of Securities Regulations as issued by the board of the Saudi Arabian Capital Market Authority, or CMA, pursuant to resolution number 2-11-2004 dated 4 October 2004 as amended by resolution number 1-28-2008, as amended, or the CMA Regulations. The CMA does not make any representation as to the accuracy or completeness of this document and expressly disclaims any liability whatsoever for any loss arising from, or incurred in reliance upon, any part of this document. Prospective purchasers of the securities offered hereby should conduct their own due diligence on the accuracy of the information relating to the securities. If you do not understand the contents of this document, you should consult an authorized financial adviser.

Notice to prospective investors in the British Virgin Islands

The shares are not being, and may not be offered to the public or to any person in the British Virgin Islands for purchase or subscription by or on behalf of us. The shares may be offered to companies incorporated under the BVI Business Companies Act, 2004 (British Virgin Islands), or BVI Companies, but only where the offer will be made to, and received by, the relevant BVI Company entirely outside of the British Virgin Islands.

Notice to prospective investors in China

This prospectus will not be circulated or distributed in the PRC and the shares will not be offered or sold, and will not be offered or sold to any person for re-offering or resale directly or indirectly to any residents of the PRC except pursuant to any applicable laws and regulations of the PRC. Neither this prospectus nor any advertisement or other offering material may be distributed or published in the PRC, except under circumstances that will result in compliance with applicable laws and regulations.

Notice to prospective investors in Korea

The shares have not been and will not be registered under the Financial Investments Services and Capital Markets Act of Korea, or the FSCMA, and the decrees and regulations thereunder and the shares have been and

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will be offered in Korea as a private placement under the FSCMA. None of the shares may be offered, sold or delivered directly or indirectly, or offered or sold to any person for re-offering or resale, directly or indirectly, in Korea or to any resident of Korea except pursuant to the applicable laws and regulations of Korea, including the FSCMA and the Foreign Exchange Transaction Law of Korea, or the FETL, and the decrees and regulations thereunder. The shares have not been listed on any securities exchanges in the world including, without limitation, the Korea Exchange in Korea. Furthermore, the purchaser of the shares shall comply with all applicable regulatory requirements (including but not limited to requirements under the FETL) in connection with the purchase of the shares. By the purchase of the shares, the relevant holder thereof will be deemed to represent and warrant that if it is in Korea or is a resident of Korea, it purchased the shares pursuant to the applicable laws and regulations of Korea.

Notice to prospective investors in Taiwan

The shares have not been and will not be registered with the Financial Supervisory Commission of Taiwan pursuant to relevant securities laws and regulations and may not be sold, issued or offered within Taiwan through a public offering or in circumstances which constitutes an offer within the meaning of the Securities and Exchange Act of Taiwan that requires a registration or approval of the Financial Supervisory Commission of Taiwan. No person or entity in Taiwan has been authorized to offer, sell, give advice regarding or otherwise intermediate the offering and sale of the shares in Taiwan.

Notice to prospective investors in South Africa

Due to restrictions under the securities laws of South Africa, no "offer to the public" (as such term is defined in the South African Companies Act, No. 71 of 2008 (as amended or re-enacted, or the South African Companies Act) is being made in connection with the issue of the shares in South Africa. Accordingly, this document does not, nor is it intended to, constitute a "registered prospectus" (as that term is defined in the South African Companies Act) prepared and registered under the South African Companies Act and has not been approved by, and/or filed with, the South African Companies and Intellectual Property Commission or any other regulatory authority in South Africa. The shares are not offered, and the offer shall not be transferred, sold, renounced or delivered, in South Africa or to a person with an address in South Africa, unless one or other of the following exemptions stipulated in section 96 (1) applies:

- Section 96 (1)(a) the offer, transfer, sale, renunciation or delivery is to:
- (i) persons whose ordinary business, or part of whose ordinary business, is to deal in securities, as principal or agent;
 - (ii) the South African Public Investment Corporation;
 - (iii) persons or entities regulated by the Reserve Bank of South Africa;
 - (iv) authorized financial service providers under South African law;
 - (v) financial institutions recognized as such under South African law;
 - (vi) a wholly-owned subsidiary of any person or entity contemplated in (c), (d) or (e), acting as agent in the capacity of an authorized portfolio manager for a pension fund, or as manager for a collective investment scheme (in each case duly registered as such under South African law); or
 - (vii) any combination of the person in (i) to (vi); or

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Section 96 (1)(b) the total contemplated acquisition cost of the securities, for any single addressee acting as principal is equal to or greater than ZAR1,000,000 or such higher amount as may be promulgated by notice in the Government Gazette of South Africa pursuant to section 96(2)(a) of the South African Companies Act.

Information made available in this prospectus should not be considered as “*advice*” as defined in the South African Financial Advisory and Intermediary Services Act, 2002.

Notice to prospective investors in Israel

This document does not constitute a prospectus under the Israeli Securities Law, 5728-1968, or the Securities Law, and has not been filed with or approved by the Israel Securities Authority. In Israel, this prospectus is being distributed only to, and is directed only at, and any offer of the shares of common stock is directed only at, (i) a limited number of persons in accordance with the Israeli Securities Law and (ii) investors listed in the first addendum, or the Addendum, to the Israeli Securities Law, consisting primarily of joint investment in trust funds, provident funds, insurance companies, banks, portfolio managers, investment advisors, members of the Tel Aviv Stock Exchange, underwriters, venture capital funds, entities with equity in excess of NIS 50 million and “qualified individuals,” each as defined in the Addendum (as it may be amended from time to time), collectively referred to as qualified investors (in each case, purchasing for their own account or, where permitted under the Addendum, for the accounts of their clients who are investors listed in the Addendum). Qualified investors are required to submit written confirmation that they fall within the scope of the Addendum, are aware of the meaning of same and agree to it.

Legal matters

The validity of the issuance of our common stock offered in this prospectus will be passed upon for us by Latham & Watkins LLP, Menlo Park, California. is acting as counsel for the underwriters in connection with this offering. Latham & Watkins LLP and certain attorneys and investment funds affiliated with the firm own an aggregate of 9,974 shares of common stock.

Experts

The financial statements incorporated in this prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2019 have been so incorporated in reliance on the report of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

Where you can find more information

We have filed with the SEC a registration statement on Form S-1 under the Securities Act with respect to the shares of common stock offered hereby. This prospectus, which constitutes a part of the registration statement, does not contain all of the information set forth in the registration statement or the exhibits and schedules filed therewith. For further information with respect to Revolution Medicines, Inc. and the common stock offered hereby, reference is made to the registration statement and the exhibits and schedules filed therewith or incorporated by reference therein. Statements contained in, or incorporated by reference in, this prospectus regarding the contents of any contract or any other document that is filed or incorporated by reference as an exhibit to the registration statement are not necessarily complete, and each such statement is qualified in all respects by reference to the full text of such contract or other document filed or incorporated by reference as an exhibit to the registration statement. The SEC also maintains a website that contains reports, proxy and information statements and other information regarding registrants that file electronically with the SEC. The address is www.sec.gov.

We are subject to the information and periodic reporting requirements of the Exchange Act and, in accordance therewith, file periodic reports, proxy statements and other information with the SEC. Such periodic reports, proxy statements and other information are available at the website of the SEC referred to above. We maintain a website at www.revmed.com. You may access our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act with the SEC free of charge at our website as soon as reasonably practicable after such material is electronically filed with, or furnished to, the SEC. The reference to our website address does not constitute incorporation by reference of the information contained on our website, and you should not consider the contents of our website in making an investment decision with respect to our common stock.

Incorporation of certain information by reference

The SEC allows us to “incorporate by reference” information from other documents that we file with it, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus. Information in this prospectus supersedes information incorporated by reference that we filed with the SEC prior to the date of this prospectus. 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. 001-39219):

- Our Annual Report on Form 10-K for the year ended December 31, 2019, filed with the SEC on March 30, 2020;
- Our Quarterly Report on Form 10-Q for the quarter ended March 31, 2020, filed with the SEC on May 14, 2020;
- Our Current Reports on Form 8-K filed with the SEC on February 18, 2020, March 20, 2020 and April 21, 2020; and
- The description of our common stock which is registered under Section 12 of the Exchange Act, in our registration statement on Form 8-A, filed on February 6, 2020, including any amendment or reports filed for the purposes of updating this description.

Notwithstanding the statements in the preceding paragraphs, no document, report or exhibit (or portion of any of the foregoing) or any other information that we have “furnished” to the SEC pursuant to the Exchange Act shall be incorporated by reference into this prospectus.

We will furnish without charge to you, on written or oral request, a copy of any or all of the documents incorporated by reference in this prospectus, including exhibits to these documents. You should direct any requests for documents to Revolution Medicines, Inc., 700 Saginaw Drive, Redwood City, CA 94063.

You also may access these filings on our website at www.revmed.com. We do not incorporate the information on our website into this prospectus or any supplement to this prospectus and you should not consider any information on, or that can be accessed through, our website as part of this prospectus or any supplement to this prospectus (other than those filings with the SEC that we specifically incorporate by reference into this prospectus or any supplement to this prospectus).

Any statement contained in a document incorporated or deemed to be incorporated by reference in this prospectus will be deemed modified, superseded or replaced for purposes of this prospectus to the extent that a statement contained in this prospectus modifies, supersedes or replaces such statement.

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shares



Common stock

Prospectus dated , 2020

PART II

Information not required in prospectus

Item 13. Other expenses of issuance and distribution.

The following table sets forth the costs and expenses, other than the underwriting discounts and commissions, payable by the registrant in connection with the sale of common stock being registered. All amounts are estimates except for the Securities and Exchange Commission, or SEC, registration fee, the FINRA filing fee and the Nasdaq Global Select Market listing fee.

Item	Amount paid or to be paid
SEC registration fee	\$
FINRA filing fee	
Printing and engraving expenses	
Legal fees and expenses	
Accounting fees and expenses	
Transfer agent fees and expenses	
Miscellaneous expenses	
Total	\$

Item 14. Indemnification of directors and officers.

As permitted by Section 102 of the Delaware General Corporation Law, we have adopted provisions in our amended and restated certificate of incorporation and bylaws that limit or eliminate the personal liability of our directors for a breach of their fiduciary duty of care as a director. The duty of care generally requires that, when acting on behalf of the corporation, directors exercise an informed business judgment based on all material information reasonably available to them. Consequently, a director will not be personally liable to us or our stockholders for monetary damages for breach of fiduciary duty as a director, except for liability for:

- any breach of the director's duty of loyalty to us or our stockholders;
- any act or omission not in good faith or that involves intentional misconduct or a knowing violation of law;
- any act related to unlawful stock repurchases, redemptions or other distributions or payment of dividends; or
- any transaction from which the director derived an improper personal benefit.

These limitations of liability do not affect the availability of equitable remedies such as injunctive relief or rescission. Our amended and restated certificate of incorporation also authorizes us to indemnify our officers, directors and other agents to the fullest extent permitted under Delaware law.

As permitted by Section 145 of the Delaware General Corporation Law, our amended and restated bylaws provide that:

- we shall indemnify our directors and officers, and may indemnify our employees and agents to the fullest extent permitted by the Delaware General Corporation Law, subject to limited exceptions;
- we shall advance expenses to our directors and officers and may advance expenses to our employees and agents in connection with a legal proceeding to the fullest extent permitted by the Delaware General Corporation Law, subject to limited exceptions; and
- the rights provided in our amended and restated bylaws are not exclusive.

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Our amended and restated certificate of incorporation and our amended and restated bylaws provide for the indemnification provisions described above and elsewhere herein. We have entered into separate indemnification agreements with our directors and officers which may be broader than the specific indemnification provisions contained in the Delaware General Corporation Law. These indemnification agreements generally require us, among other things, to indemnify our officers and directors against liabilities that may arise by reason of their status or service as directors or officers, other than liabilities arising from willful misconduct. These indemnification agreements also generally require us to advance any expenses incurred by the directors or officers as a result of any proceeding against them as to which they could be indemnified. In addition, we have purchased a policy of directors' and officers' liability insurance that insures our directors and officers against the cost of defense, settlement or payment of a judgment in some circumstances. These indemnification provisions and the indemnification agreements may be sufficiently broad to permit indemnification of our officers and directors for liabilities, including reimbursement of expenses incurred, arising under the Securities Act of 1933, as amended, or the Securities Act.

The form of Underwriting Agreement, to be attached as Exhibit 1.1 hereto, provides for indemnification by the underwriters of us and our officers who sign this Registration Statement and directors for specified liabilities, including matters arising under the Securities Act.

Item 15. Recent sales of unregistered securities.

The following list sets forth information as to all securities we have sold since January 1, 2017, which were not registered under the Securities Act.

1. In April and May 2017, we issued an aggregate of 4,663,747 shares of Series A preferred stock to 5 accredited investors at a price per share of \$4.87, for a total amount raised of \$22.7 million.
2. In March and June 2018, we issued an aggregate of 7,731,155 shares of Series B preferred stock to 17 accredited investors at a price per share of \$7.30, for a total amount raised of \$56.4 million.
3. In October 2018, we issued an aggregate of 6,797,915 shares of Series B preferred stock to 91 accredited investors pursuant to our acquisition of Warp Drive Bio, Inc.
4. In October 2018, we issued an aggregate of 200,493 shares of Series B preferred stock to one accredited investor at a price per share of \$10.03 pursuant to the conversion of a promissory note.
5. In November 2018, we issued an aggregate of 435,544 shares of Series B preferred stock to eight accredited investors at a price per share of \$10.03, for a total amount raised of \$4.4 million.
6. In June and July 2019, we issued an aggregate of 10,004,514 shares of Series C preferred stock to 34 accredited investors at a price per share of \$10.03, for a total amount raised of \$100.3 million.
7. We granted stock options and stock awards to employees, directors and consultants covering an aggregate of 6,696,482 shares of common stock, at a weighted-average exercise price of \$4.58 per share. Of these, options covering an aggregate of 236,254 shares were cancelled without being exercised.
8. We sold an aggregate of 1,416,217 shares of common stock to employees, directors and consultants for cash consideration in the aggregate amount of \$1.1 million pursuant to stock options and restricted stock awards.

We claimed exemption from registration under the Securities Act for the sale and issuance of securities in the transactions described in paragraphs (1) through (5) by virtue of Section 4(a)(2) and/or Regulation D promulgated thereunder as transactions not involving any public offering. All of the purchasers of unregistered

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securities for which we relied on Section 4(a)(2) and/or Regulation D represented that they were accredited investors as defined under the Securities Act. We claimed such exemption on the basis that (a) the purchasers in each case represented that they intended to acquire the securities for investment only and not with a view to the distribution thereof and that they either received adequate information about the registrant or had access, through employment or other relationships, to such information and (b) appropriate legends were affixed to the stock certificates issued in such transactions.

We claimed exemption from registration under the Securities Act for the sales and issuances of securities in the transactions described in paragraphs (6) and (7) above under Section 4(a)(2) of the Securities Act in that such sales and issuances did not involve a public offering or under Rule 701 promulgated under the Securities Act, in that they were offered and sold either pursuant to written compensatory plans or pursuant to a written contract relating to compensation, as provided by Rule 701.

Item 16. Exhibits and financial statement schedules.**(a) Exhibits.**

Exhibit number	Exhibit description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
1.1*	Form of Underwriting Agreement.				
2.1	Agreement and Plan of Merger, dated as of October 15, 2018, by and among Revolution Medicines, Inc., Trotsky Merger Sub, Inc., Warp Drive Bio, Inc., and Fortis Advisors LLC.	S-1	1/17/2020	2.1	
3.1	Amended and Restated Certificate of Incorporation.	8-K	2/18/2020	3.1	
3.2	Amended and Restated Bylaws.	8-K	2/18/2020	3.2	
4.1	Reference is made to Exhibits 3.1 through 3.2 .				
4.2	Form of Common Stock Certificate.	S-1	1/17/2020	4.2	
5.1*	Opinion of Latham & Watkins LLP.				
10.1†	Collaborative Research, Development and Commercialization Agreement, dated as of June 8, 2018, by and between Revolution Medicines, Inc. and Aventis, Inc., as amended.	S-1	1/17/2020	10.1	
10.2	Amended and Restated Investors' Rights Agreement, dated as of June 5, 2019, by and among Revolution Medicines, Inc. and the investors listed therein.	S-1	1/17/2020	10.2	
10.3A	Lease between HCP LS Redwood City, LLC and Revolution Medicines, Inc., dated as of January 15, 2015.	S-1	1/17/2020	10.3A	
10.3B	First Amendment to Lease by and between HCP LS Redwood City, LLC and Revolution Medicines, Inc., dated as of September 16, 2016.	S-1	1/17/2020	10.3B	
10.3C	Sublease between OncoMed Pharmaceuticals, Inc. and Revolution Medicines, Inc., dated as of January 16, 2019.	S-1	1/17/2020	10.3C	

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Exhibit number	Exhibit description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
10.3D	Second Amendment to Lease by and between HCP LS Redwood City, LLC and Revolution Medicines, Inc., dated as of April 17, 2020.	10-Q	5/14/2020	10.4	
10.4A	Lease Agreement between Are-Tech Square, LLC and Warp Drive Bio, LLC, dated as of August 22, 2012.	S-1	1/17/2020	10.4A	
10.4B	First Amendment to Lease by and between Are-Tech Square, LLC and Warp Drive Bio, Inc., dated as of May 18, 2017.	S-1	1/17/2020	10.4B	
10.5A	Assignment and Assumption of Lease by and between Warp Drive Bio, LLC and Revolution Medicines, Inc., dated as of January 30, 2019.	S-1	1/17/2020	10.5A	
10.5B	Sublease Agreement between Revolution Medicines, Inc., as successor to Warp Drive Bio, LLC, and Casma Therapeutics, Inc., dated as of February 4, 2019.	S-1	1/17/2020	10.5B	
10.6(a)#	2014 Equity Incentive Plan, as amended.	S-1	1/17/2020	10.6(a)	
10.6(b)#	Form of Amended and Restated Early Exercise Stock Option Grant Notice and Amended and Restated Stock Option Agreement under 2014 Equity Incentive Plan, as amended.	S-1	1/17/2020	10.6(b)	
10.7(a)#	2020 Incentive Award Plan.	S-1/A	2/3/2020	10.7(a)	
10.7(b)#	Form of Stock Option Grant Notice and Stock Option Agreement under the 2020 Incentive Award Plan.	S-1/A	2/3/2020	10.7(b)	
10.7(c)#	Form of Restricted Stock Award Agreement under the 2020 Incentive Award Plan.	S-1/A	2/3/2020	10.7(c)	
10.7(d)#	Form of Restricted Stock Unit Award Grant Notice under the 2020 Incentive Award Plan.	S-1/A	2/3/2020	10.7(d)	
10.8#	2020 Employee Stock Purchase Plan.	S-1/A	2/3/2020	10.8	
10.9#	Employment Agreement by and between Revolution Medicines, Inc. and Mark A. Goldsmith, M.D., Ph.D.	S-1	1/17/2020	10.9	
10.10#	Employment Agreement by and between Revolution Medicines, Inc. and Steve Kelsey, M.D., FRCP, FRCPath.	S-1	1/17/2020	10.10	
10.11#	Employment Agreement by and between Revolution Medicines, Inc. and Margaret Horn, J.D.	S-1	1/17/2020	10.11	
10.12#	Non-Employee Director Compensation Program.	S-1/A	2/3/2020	10.12	
10.13	Form of Indemnification Agreement for directors and officers.	S-1/A	2/3/2020	10.13	
21.1	Subsidiaries of Registrant.	S-1	1/17/2020	21.1	
23.1*	Consent of Independent Registered Public Accounting Firm.				
23.2*	Consent of Latham & Watkins LLP (included in Exhibit 5.1).				
24.1*	Power of Attorney.				

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- † Portions of the exhibit, marked by brackets, have been omitted because the omitted information (i) is not material and (ii) would likely cause competitive harm if publicly disclosed.
Indicates management contract or compensatory plan.
* To be filed by amendment.

(b) Financial Statement Schedules. Schedules not listed above have been omitted because the information required to be set forth therein is not applicable or is shown in the financial statements or notes thereto.

Item 17. Undertakings.

Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the Registrant pursuant to the foregoing provisions, or otherwise, the Registrant has been advised that in the opinion of the SEC such indemnification is against public policy as expressed in the Securities Act, and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the Registrant of expenses incurred or paid by a director, officer, or controlling person of the Registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the Registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question of whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

The undersigned Registrant hereby undertakes that:

1. For purposes of determining any liability under the Securities Act, the information omitted from the form of prospectus filed as part of this Registration Statement in reliance upon Rule 430A and contained in a form of prospectus filed by the Registrant pursuant to Rule 424(b) (1) or (4) or 497(h) under the Securities Act shall be deemed to be part of this Registration Statement as of the time it was declared effective.
2. For the purpose of determining any liability under the Securities Act, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

The undersigned Registrant hereby undertakes to provide to the underwriters at the closing specified in the underwriting agreement certificates in such denominations and registered in such names as required by the underwriters to permit prompt delivery to each purchaser.

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Signatures

Pursuant to the requirements of the Securities Act of 1933, as amended, the Registrant has duly caused this Registration Statement on Form S-1 to be signed on its behalf by the undersigned, thereunto duly authorized, in Redwood City, California on _____, 2020.

Revolution Medicines, Inc.

By: _____
Mark A. Goldsmith, M.D., Ph.D.
President and Chief Executive Officer

Power of attorney

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below hereby constitutes and appoints Mark A. Goldsmith, M.D., Ph.D., Margaret A. Horn, J.D., and Jack Anders, and each of them acting individually, as his or her true and lawful attorneys-in-fact and agents, each with full power of substitution, for him in any and all capacities, to sign any and all amendments to this Registration Statement, including post-effective amendments or any abbreviated registration statement and any amendments thereto filed pursuant to Rule 462(b) increasing the number of securities for which registration is sought, and to file the same, with all exhibits thereto and other documents in connection therewith, with the SEC, granting unto said attorneys-in-fact and agents, with full power of each to act alone, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully for all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or his, her or their substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act, this Registration Statement has been signed by the following persons in the capacities and on the dates indicated.

Signature	Title	Date
_____ Mark A. Goldsmith, M.D., Ph.D.	President, Chief Executive Officer and Director <i>(Principal Executive Officer)</i>	, 2020
_____ Jack Anders	Vice President, Finance and Principal Accounting Officer <i>(Principal Financial and Accounting Officer)</i>	, 2020
_____ Elizabeth McKee Anderson	Director	, 2020
_____ Alexis Borisy	Director	, 2020
_____ Neil Exter	Director	, 2020

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Signature	Title	Date
_____ Larry Lasky, Ph.D.	Director	, 2020
_____ Vincent A. Miller, M.D.	Director	, 2020
_____ Thilo Schroeder, Ph.D.	Director	, 2020
_____ Barbara Weber, M.D.	Director	, 2020