MERRIMACK PHARMACEUTICALS INC
Form 10-K
February 26, 2016
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**UNITED STATES**

**SECURITIES AND EXCHANGE COMMISSION**

**WASHINGTON, D.C. 20549**

# FORM 10-K

**(Mark One)**

x **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

**For the fiscal year ended December 31, 2015**

**or**

¨ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

**For the transition period from to**

**Commission file number 001-35409**

**Merrimack Pharmaceuticals, Inc.**

**(Exact name of registrant as specified in its charter)**

| | |
|---|---|
| **Delaware** | **04-3210530** |
| **(State or other jurisdiction of** | **(I.R.S. Employer** |
| **incorporation or organization)** | **Identification No.)** |
| **One Kendall Square, Suite B7201** | |
| **Cambridge, MA** | **02139** |
| **(Address of principal executive offices)** | **(Zip Code)** |

**Registrant s telephone number, including area code: (617) 441-1000**

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

| **Title of each class** | **Name of each exchange on which registered** |
|---|---|
| **Common Stock, $0.01 par value** | **NASDAQ Global Market** |

**Securities registered pursuant to Section 12(g) of the Act: None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. x Yes ¨ No

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. ¨ Yes x No

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. x Yes ¨ No

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). x Yes ¨ No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. x

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 and smaller reporting company in Rule 12b-2 of the Exchange Act.

| | | | |
|---|---|---|---|
| Large accelerated filer | x | Accelerated filer | ¨ |
| Non-accelerated filer | ¨ (Do not check if a smaller reporting company) | Smaller reporting company | ¨ |

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

Aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant, based on the last sale price for such stock on June 30, 2015: $1,286,139,750.

As of February 15, 2016, there were 116,060,572 shares of Common Stock, $0.01 par value per share, outstanding.

**DOCUMENTS INCORPORATED BY REFERENCE**

The registrant intends to file a definitive proxy statement pursuant to Regulation 14A in connection with its 2016 Annual Meeting of Stockholders. Portions of such proxy statement are incorporated by reference into Part III of this Annual Report on Form 10-K.

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## FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Annual Report on Form 10-K, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words anticipate, believe, estimate, expect, intend, may, plan, predict, project, target, potential, will, would, could, s expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this Annual Report on Form 10-K include, among other things, statements about:

- the market potential and our commercialization efforts for MM-398, which is marketed by us in the United States under the brand name ONIVYDE®;
- our plans to develop and commercialize our clinical stage product candidates and diagnostics;
- our ongoing and planned discovery programs, preclinical studies and clinical trials;
- the timing of the completion of our clinical trials and the availability of results from such trials;
- our collaborations with Baxalta Incorporated, Baxalta US Inc. and Baxalta GmbH, which we collectively refer to as Baxalta, and PharmaEngine, Inc., or PharmaEngine, related to ONIVYDE;
- our ability to establish and maintain additional collaborations;
- the timing of and our ability to obtain and maintain regulatory approvals for our products and product candidates;
- the rate and degree of market acceptance and clinical utility of our products;
- our intellectual property position;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the potential advantages of our systems biology approach to drug research and development;

the potential use of our systems biology approach in fields other than oncology; and

our estimates regarding expenses, future revenues, capital requirements and needs for additional financing.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in Part I, Item 1A. Risk Factors, that could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments that we may make.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

**NOTE REGARDING TRADEMARKS**

ONIVYDE® is a registered trademark of Merrimack Pharmaceuticals, Inc. Any other trademarks, trade names and service marks referred to in this Annual Report on Form 10-K are the property of their respective owners.

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# PART I

## Item 1. Business

### Overview

We are a biopharmaceutical company discovering, developing and commercializing innovative medicines consisting of novel therapeutics paired with diagnostics for the treatment of cancer. We were founded by a team of scientists from The Massachusetts Institute of Technology and Harvard University who sought to develop a systems biology-based approach to biomedical research. The core of our approach to systems biology is to apply multidisciplinary and multitechnology capabilities to build functional and predictive computational models of biological systems, such as cell signaling networks, that allow us to engineer treatments that are directed at the mechanisms of disease. We view cancer as a complex engineering challenge. Through systems biology, which brings together the fields of biology, computing and engineering, we aim to decrease uncertainty in drug development and clinical validation, and move discovery efforts beyond trial and error. Our mission is to employ these insights to provide patients, physicians and the healthcare system with the medicines, tools and information to deliver integrated healthcare solutions that improve both the quality of outcomes and the efficiency of care.

We have one marketed therapeutic oncology product and multiple targeted therapeutic oncology candidates in clinical development. Our most advanced program is our therapeutic MM-398, which we market in the United States under the brand name ONIVYDE. On October 22, 2015, the U.S. Food and Drug Administration, or FDA, and the Taiwan Food and Drug Administration, or TFDA, approved the use of ONIVYDE in combination with fluorouracil, or 5-FU, and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy in the United States and Taiwan, respectively. In addition, the European Medicines Agency, or EMA, has accepted for review a Marketing Authorization Application, or MAA, filed by our collaboration partner Baxalta for ONIVYDE in combination with 5-FU and leucovorin for the treatment of adult patients with metastatic adenocarcinoma of the pancreas who have been previously treated with gemcitabine-based therapy.

In addition to ONIVYDE and our product candidates in clinical development, we have multiple product candidates in preclinical development and a discovery effort advancing additional candidate medicines. We have tailored ONIVYDE and our other product candidates to target specific disease mechanisms that our research suggests are common across many solid tumor types. We believe that ONIVYDE and our other product candidates have the potential to address major unmet medical needs.

We are also developing *in vitro* and *in vivo* diagnostics for use with each of our oncology therapeutic product candidates. Our *in vitro* diagnostic agents employ biophysical or biochemical markers of cancer, or biomarkers, which we have identified using our systems biology approach. Our *in vivo* diagnostics take the form of imaging agents that may help identify patients likely to benefit from our therapeutic products by measuring deposition of our products in the tumor. We believe that diagnostics will allow us to improve the efficiency and productivity of our clinical development and enhance the potential efficacy and pharmacoeconomic benefit of our therapeutics.

We have also entered into an agreement to utilize our manufacturing expertise to develop, manufacture and exclusively supply bulk drug product to a third party, who will in turn process the drug into finished product and commercialize it globally following regulatory approval.

### Our Most Advanced Product Candidates

The table and descriptions below summarize key information about ONIVYDE (MM-398) and our other clinical stage product candidates, MM-302, MM-121, MM-141 and MM-151. Each of the product candidates described below is a targeted therapy, designed to efficiently act on selected cancer cells. These targeted therapies are either designed to deliver cytotoxic therapies to the tumor tissue, such as ONIVYDE and MM-302, or are monoclonal antibodies or monoclonal antibody-derived molecules that are designed to block oncogenic signaling pathways, such as MM-121, MM-141 and MM-151. Other than ONIVYDE, none of our product candidates are approved for any indication by the FDA or any other regulatory agency.

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| Program | Status | Commercial Rights (Territory) |
|---|---|---|
| **ONIVYDE (MM-398)**<br><br>(irinotecan liposome injection) | Approved by the FDA and TFDA in combination with 5-FU and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy in the United States and Taiwan, respectively | Merrimack (United States)<br><br>PharmaEngine (Taiwan) |
| | Launched commercially in the United States on October 26, 2015 | Baxalta (rest of world outside of United States and Taiwan) |
| | Pending EMA MAA (filed by Baxalta) for ONIVYDE in combination with 5-FU and leucovorin for the treatment of adult patients with metastatic adenocarcinoma of the pancreas who have been previously treated with gemcitabine-based therapy | |
| | Conducting a Phase 2 clinical trial in combination with 5-FU and leucovorin in patients with previously untreated, metastatic pancreatic adenocarcinoma | |
| | Ongoing Phase 1 clinical trials: as a monotherapy in patients with glioma, in combination with cyclophosphamide in patients with pediatric solid tumors and in combination with standard irinotecan in gastrointestinal tumors | |
| | Conducting a Phase 1 translational clinical trial in metastatic breast cancer designed to identify predictive biomarkers associated with MM-398 | |
| **MM-302** | Conducting a Phase 2 clinical trial in combination with trastuzumab in patients with ErbB2 (HER2) positive, locally advanced or metastatic breast cancer | Merrimack (worldwide) |

| | | |
|---|---|---|
| (ErbB2 (HER2) targeted antibody drug conjugated liposomal doxorubicin) | Announced final results for a Phase 1 clinical trial in April 2015 | |
| **MM-121**<br><br>(seribantumab) (ErbB3 targeted monoclonal antibody) | Conducting a Phase 2 clinical trial in combination with docetaxel or pemetrexed in patients with heregulin positive, advanced non-small cell lung cancer | Merrimack (worldwide) |
| **MM-141**<br><br>(istiratumab) (IGF-1R and ErbB3 targeted tetravalent bispecific antibody) | Conducting a Phase 2 clinical trial in combination with nab-paclitaxel and gemcitabine in previously untreated metastatic pancreatic cancer patients who have high serum levels of free IGF-1 | Merrimack (worldwide) |
| | Conducting a Phase 1 clinical trial as a monotherapy, in combination with everolimus and in combination with nab-paclitaxel and gemcitabine in patients with solid tumors | |
| **MM-151**<br><br>(EGFR (ErbB1) targeted oligoclonal antibody) | Completed a Phase 1 clinical trial as a monotherapy and in combination with irinotecan in patients with solid tumors | Merrimack (worldwide) |

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**ONIVYDE® (MM-398)**

***ONIVYDE (MM-398) overview***

ONIVYDE (irinotecan liposome injection), also known as MM-398, is a novel encapsulation of the marketed chemotherapy drug irinotecan in a liposomal formulation. On October 22, 2015, the FDA and the TFDA approved the use of ONIVYDE in combination with 5-FU and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy in the United States and Taiwan, respectively. ONIVYDE is the first and only FDA-approved therapy in this setting. ONIVYDE is not indicated for use as a single agent. In addition, among other pending applications before regulatory authorities in foreign jurisdictions, the EMA has accepted for review an MAA filed by Baxalta for ONIVYDE in combination with 5-FU and leucovorin for the treatment of adult patients with metastatic adenocarcinoma of the pancreas who have been previously treated with gemcitabine-based therapy.

We hold development and commercialization rights for ONIVYDE in the United States. In September 2014, we established a collaboration with Baxalta for the development and commercialization of ONIVYDE outside of the United States and Taiwan. PharmaEngine holds the development and commercialization rights to ONIVYDE in Taiwan. We believe that ONIVYDE may have potential uses in a number of other solid tumor indications beyond its currently approved indication, and additional clinical trials of ONIVYDE are ongoing or in the planning stages.

ONIVYDE has obtained orphan drug exclusivity in the United States from the FDA for the treatment of pancreatic cancer, and orphan medicinal product designation in the European Union from the EMA for the treatment of pancreatic cancer. In addition, ONIVYDE is covered by multiple patents and trademarks worldwide.

***ONIVYDE (MM-398) Phase 3 clinical trial for metastatic adenocarcinoma of the pancreas***

The basis of the recent FDA and TFDA approvals of ONIVYDE in combination with 5-FU and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy was our randomized, open label Phase 3 clinical trial of MM-398 in patients with metastatic adenocarcinoma of the pancreas who received prior gemcitabine-based therapy. We refer to this clinical trial as the NAPOLI-1 trial. Patients were enrolled at 76 sites in North America, South America, Europe, Asia and Oceania. The trial evaluated ONIVYDE in combination with 5-FU and leucovorin administered every two weeks and as a monotherapy administered every three weeks. Each ONIVYDE containing arm was compared to a control arm of 5-FU and leucovorin. A total of 417 patients were randomized across the three arms. The primary endpoint of the trial was overall survival. Overall survival is a measure of the time to death from treatment randomization. Primary survival analysis was based on 313 events and showed that ONIVYDE in combination with 5-FU and leucovorin significantly improved overall survival versus 5-FU and leucovorin alone: 6.1 months versus 4.2 months (p=0.012, unstratified hazard ratio=0.67, 95% CI: [0.49-0.92]). The monotherapy regimen in this trial did not show improvement over the 5-FU and leucovorin arm: 4.9 months versus 4.2 months (p=0.94, HR=0.99, 95% CI: [0.77-1.28]). A hazard ratio, or HR, is a measure of how often a particular event happens in one group compared to how often it happens in another group over time. In cancer research, hazard ratios are often used in clinical trials to measure survival at any point in time in a group of patients who have been given a specific treatment compared to a control group given another treatment or a placebo. A hazard ratio of one means that there is no difference in survival between the two groups, while a hazard ratio of greater than one or less than one means that survival was better in one of the groups. The confidence interval, or CI, given after the HR reflects the amount of certainty in the estimate of the HR. An HR value that is not contained within a 95% CI is unlikely to be the true HR. ONIVYDE in combination with 5-FU and leucovorin also achieved a longer progression-free survival compared with the 5-FU and leucovorin arm (3.1 months versus 1.5 months; unstratified HR=0.56). The most common non-hematologic grade 3 and higher adverse events in

the ONIVYDE combination arm were fatigue (14%), diarrhea (13%) and vomiting (11.1%). Hematologic grade 3 and higher adverse events included neutropenia, which was observed in 20% of patients as determined by objective laboratory values, and febrile neutropenia, which was observed in 2% of patients.

In January 2016, we announced an updated overall survival analysis from our NAPOLI-1 clinical trial. The updated data analysis was based on 378 events and included data from all patients randomized across the three arms of the trial. Twelve-month survival estimates for ONIVYDE in combination with 5-FU and leucovorin were 26% (95% CI, 18-35%) compared to 16% (95% CI, 10-24%) for 5-FU and leucovorin alone. Six-month survival estimates were 53% (95% CI, 44-62%) for the ONIVYDE combination regimen versus 38% (95% CI, 29-47%) for 5-FU and leucovorin. No new safety or tolerability concerns were noted in the updated data analysis. The most common grade 3 and higher adverse events occurring at a 2% or greater incidence in the ONIVYDE containing arms were neutropenia (ONIVYDE monotherapy arm: 15%; ONIVYDE + 5-FU/LV arm: 28%), diarrhea (ONIVYDE monotherapy arm: 21%; ONIVYDE + 5-FU/LV arm: 13%), vomiting (ONIVYDE monotherapy arm: 14%; ONIVYDE + 5-FU/LV arm: 12%) and fatigue (ONIVYDE monotherapy arm: 6%; ONIVYDE + 5-FU/LV arm: 14%).

***MM-398 Phase 2 clinical trial in front-line metastatic pancreatic cancer***

In October 2015, we enrolled the first patient in a Phase 2 clinical trial of MM-398 in front-line metastatic pancreatic cancer. This trial is designed to assess the safety and efficacy of the combination of MM-398 plus 5-FU and leucovorin, with or without the addition of oxaliplatin, versus nab-paclitaxel and gemcitabine in patients with previously untreated, metastatic pancreatic

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adenocarcinoma. The trial will be conducted in two parts. In the first part of the trial, we expect to enroll approximately six to18 patients. The primary outcome for Part 1 of the trial is to evaluate the safety and tolerability of ONIVYDE in combination with 5-FU and leucovorin and oxaliplatin. In the second part of the trial, we expect an additional 150 patients (50 patients per arm) with previously untreated, metastatic pancreatic adenocarcinoma will be enrolled and randomized to receive ONIVYDE in combination with 5-FU and leucovorin and oxaliplatin, ONIVYDE in combination with 5-FU and leucovorin or nab-paclitaxel and gemcitabine. In Part 2 of the trial, efficacy of the ONIVYDE containing regimens will be compared to the nab-paclitaxel and gemcitabine regimen, evaluating progression free survival, or PFS, at 24 weeks, as well as overall survival, objective response rate, tumor marker CA19-9 response, safety and tolerability. PFS is the time from the initiation of treatment to tumor progression based on an increase of at least 20% in the sum of measured tumor diameters with no new tumors. The trial will be conducted at sites in the United States, Canada, Europe, Australia, New Zealand, Taiwan and South Korea.

***MM-398 other clinical trials***

We are also collaborating with several investigators to conduct additional trials of MM-398, including in a Phase 1 clinical trial in gastrointestinal tumors, a Phase 1 clinical trial utilizing a high concentration formulation of MM-398 in patients with glioma and a Phase 1 clinical trial in pediatric solid tumors.

***MM-398 diagnostic development***

We believe that deposition of MM-398 in the tumor may be important to efficacy. We are exploring development of *in vivo* diagnostics that take the form of imaging agents that may serve as surrogate biomarkers for estimating MM-398 deposition in patient tumors. The diagnostic may help identify patients most likely to benefit from MM-398, and direct those patients with low deposition tumors towards alternate therapy strategies. We are currently evaluating various agents imaged by MRI and other modalities to assess the potential for predicting drug deposition. We recently initiated an expansion of a Phase 1 translational study designed to assess the feasibility of using an MRI-based approach with a marketed iron supplement used off-label as an imaging agent to act as a marker for MM-398 tumor response prediction. The expansion phase of this study will enroll patients who have metastatic breast cancer that is hormone receptor positive, triple negative or where active brain metastases are present. As part of our preclinical and clinical translational research, we are also investigating functional *in vitro* biomarkers that may be predictive of efficacy in poorly vascularized tumors.

**MM-302**

***MM-302 overview***

MM-302 is an antibody drug conjugated liposomal doxorubicin that targets the ErbB2 (HER2) receptor. Doxorubicin is a marketed chemotherapy that is a member of the anthracycline class of chemotherapeutics. As a liposomal encapsulation of doxorubicin, MM-302 is designed to target and bind to cancer cells that overexpress ErbB2 (HER2) to allow for the selective uptake of drug into tumor cells while minimizing exposure to healthy tissues, such as those of the heart. Unlike other HER2 targeted agents, MM-302 is not designed to inhibit HER2 signaling pathways and relies on HER2 as a means to identify and gain access to the cancer cells.

We believe that MM-302 may offer advantages in comparison with other forms of doxorubicin, namely free doxorubicin and liposomal doxorubicin. Our clinical development strategy is to demonstrate that MM-302 has favorable efficacy and safety for the treatment of metastatic breast cancer where concerns over cardiac safety, particularly in combination with trastuzumab, have led to a decline in the use of anthracyclines despite proven efficacy.

***MM-302 Phase 2 clinical trial in metastatic breast cancer***

In August 2014, we initiated a global, open-label, randomized Phase 2 clinical trial of MM-302 in combination with trastuzumab (Herceptin®) in patients with ErbB2 (HER2) positive, locally advanced or metastatic breast cancer. The trial was designed with input from the FDA to support a potential accelerated approval application. The trial has also been reviewed by the EMA, and we intend to use data from the trial, if positive, to support conditional marketing authorization in Europe. This clinical trial, which we refer to as the HERMIONE trial, is expected to enroll approximately 250 patients who will be randomized (1:1) to receive either MM-302 and trastuzumab or chemotherapy of their physician s choice (capecitabine, gemcitabine or vinorelbine) and trastuzumab. Eligible patients for the HERMIONE trial must have received prior treatment with trastuzumab in any setting, and pertuzumab (Perjeta®) and ado-trastuzumab emtansine (T-DM1, Kadcyla®) in the locally advanced or metastatic setting, but have not been treated with an anthracycline-based regimen. The primary endpoint of the trial is PFS. Secondary endpoints include overall survival, objective response rate, safety and tolerability. The trial will be conducted at approximately 110 sites in the United States, Canada and Europe.

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Prior to initiating the HERMIONE trial, we conducted a Phase 1 clinical trial of MM-302 in patients with advanced ErbB2 (HER2) positive breast cancer. The purpose of that Phase 1 clinical trial was to assess the safety of MM-302 and identify the maximum tolerated dose. In April 2015, we reported final results from this trial showing that the group of patients (n=62) treated with 30 mg/m2 or more of MM-302 alone, in combination with trastuzumab or with trastuzumab and cyclophosphamide, had a median progression free survival, or mPFS, of 7.6 months (95% CI: 3.6-10.9 months) and an overall response rate, or ORR, of 11%. Patients who had not been previously treated with anthracyclines (n=25) had an mPFS of 11 months (95% CI: 1.8-13.1 months) and an ORR of 24%. The most frequent adverse events occurring in greater than 20% of the population in this trial were constipation (29%), cough (25%), decreased appetite (29%), diarrhea (23%), dyspnea (20%), fatigue (49%), nausea (49%), neutropenia (22%), stomatitis (22%) and vomiting (26%). The most common grade 3/4 adverse event was neutropenia, which was observed in eight patients. Six out of 69 patients (9%) had protocol-defined asymptomatic declines in left ventricular ejection fraction, four of which had reversible declines consistent with trastuzumab-induced changes. One patient experienced two reversible asymptomatic left ventricular ejection fraction declines (classified as a grade 1 cardiac failure) that resulted in treatment discontinuation after receiving 11 cycles of MM-302 in combination with trastuzumab. Patients treated with MM-302 as a monotherapy showed no signs of protocol-defined decline in cardiac function.

***MM-302 diagnostic development***

We believe that deposition of nanotherapeutics such as MM-302 in the tumor may be important to efficacy. We are exploring development of *in vivo* diagnostics that take the form of imaging agents that may help identify patients likely to benefit from nanotherapeutics by enabling the measurement of deposition in patient tumors and excluding those patients with low deposition whose tumors are therefore unlikely to respond to treatment with a nanotherapeutic. We are currently evaluating nanotherapeutic formulations of liposomal agents imaged by PET/CT scan and other modalities to assess the potential for measuring deposition.

**MM-121 (seribantumab)**

***MM-121 overview***

MM-121 is a fully human monoclonal antibody that targets ErbB3, a cell surface receptor that is activated by its ligand heregulin. Heregulin-driven ErbB3 signaling has been implicated as a mechanism of tumor growth and resistance to targeted, cytotoxic and anti-endocrine therapies. When used in combination with cytotoxic chemotherapeutics, MM-121 is designed to block ErbB3 signaling in order to restore or enhance the anti-tumor effect of a combination therapy partner.

Based on the central role of heregulin and ErbB3 in cancer growth and survival, we believe that MM-121 may be applicable to a broad range of metastatic tumors, including lung, prostate, breast, ovarian, colon and pancreatic cancers. Our preclinical studies of several hundred tumor samples and the analysis of tumor samples from our Phase 2 clinical trials suggest that MM-121 may be able to target heregulin-dependent ErbB3 signaling that is relevant in approximately 35-50% or more of cancer patients with these types of tumors.

***MM-121 Phase 2 clinical trial in metastatic non-small cell lung cancer***

In February 2015, we initiated a global, open-label, biomarker-selected, randomized Phase 2 clinical trial of MM-121 in combination with docetaxel or pemetrexed versus docetaxel or pemetrexed alone in patients with heregulin positive, locally advanced or metastatic non-small cell lung cancer. In December 2015, we announced an amendment to the trial, including a change in primary endpoint from PFS to overall survival. This trial is expected to enroll approximately 280 heregulin positive patients who will be randomized (2:1) to receive MM-121 plus the investigator s

choice of docetaxel or pemetrexed, or the investigator s choice of docetaxel or pemetrexed alone, at sites in the United States, Canada, Asia and Europe. Eligible patients for the trial must have failed prior treatment with no more than three lines of therapy for locally advanced or metastatic disease including, where applicable, with therapies directed against immune checkpoints, such as programmed death-ligand 1 (PD-L1) or its receptor, programmed death 1 (PD-1). The primary endpoint of the trial is overall survival. Secondary endpoints include PFS, objective response rate, safety and quality of life measures.

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***MM-121 previous clinical trials***

We have evaluated MM-121 in multiple Phase 1 and Phase 2 clinical trials in combination with both chemotherapies and other targeted agents across a wide spectrum of solid tumor patient populations, including patients with ovarian, breast and lung cancers. The goal of our MM-121 clinical program is to explore the efficacy and safety of MM-121 in combination with other targeted ErbB agents and to establish and validate clinically meaningful biomarkers that were initially identified using our systems biology approach to identify patients most likely to benefit from MM-121.

Three such previous Phase 2 clinical trials of MM-121 in non-small cell lung cancer, ovarian cancer and breast cancer enrolled a total of 464 patients and evaluated whether MM-121 in combination with a standard of care therapy was more effective than the standard of care therapy alone in prolonging PFS. In the non-small cell lung cancer trial, two of the three cohorts (Groups A and C) did not meet their primary endpoints, and the third cohort (Group B) did not pass its planned interim analysis and ceased enrolling patients. Additionally, we did not meet the primary endpoints in the clinical trials of MM-121 in patients with ovarian cancer or in patients with breast cancer, although our biomarker analysis in each trial identified a potential subpopulation of patients benefiting from MM-121 in combination with either paclitaxel or exemestane, respectively. As ErbB3 signaling was expected to be active in only a subset of patients, pre-treatment biopsies were collected from patients in the lung and ovarian studies and archived tumor tissue in all three studies to assess heregulin, along with four other pre-specified biomarkers. Secondary analyses included evaluation of the pre-specified biomarkers, as well as overall survival and safety data. Across the trials, there was a consistent but modest and tolerable increase in adverse events when MM-121 was combined with erlotinib, paclitaxel and exemestane. Most adverse events were reported as mild to moderate in severity and included diarrhea, fatigue, vomiting, rash, hypokalemia and stomatitis.

***MM-121 diagnostic development***

We are developing a diagnostic that is focused on measuring certain mechanistically related biomarkers to determine whether a tumor is dependent on ErbB3 signaling and therefore amenable to treatment with MM-121. In 2014, we announced updated biomarker results from a meta-analysis of three randomized clinical trials of MM-121 in patients with ovarian, breast and lung cancers. This analysis included biomarker and efficacy results that had previously been disclosed, as well as additional biomarker data from the Phase 2 metastatic breast cancer trial that had not previously been reported. This meta-analysis highlighted heregulin as the principal biomarker for MM-121 efficacy. High levels of heregulin mRNA correlated with favorable hazard ratios in all three settings: in ovarian cancer, heregulin-high patients had a PFS HR of 0.37 (95% CI [0.18  0.76]) (57 of 151 evaluable patients; prevalence of 38%); in breast cancer, heregulin-high patients had a PFS HR of 0.26 (95% CI [0.11  0.63]) (34 of 76 evaluable patients; prevalence of 45%); in lung cancer, heregulin-high patients had a PFS HR of 0.35 (95% CI [0.16  0.76]) (37 of 69 evaluable patients; prevalence of 54%). In ovarian cancer, the definition of biomarker positive also required that patients have low ErbB2 (HER2) levels. In breast cancer, where only ErbB2 (HER2) negative patients were enrolled in the clinical trial, this requirement was not needed. In lung cancer, where ErbB2 (HER2) levels are naturally low, this requirement was also not needed.

Heregulin mRNA was measured in two different ways in the Phase 2 clinical trials. For archived tissue samples obtained through surgical removal of tumor tissue, which was the source of tissue in the breast cancer clinical trial, heregulin mRNA was measured by reverse transcriptase polymerase chain reaction (RT-PCR). This is a commonly used quantitative assay that provides a measure of the amount of heregulin mRNA in a block of tissue. In tissue samples obtained through a biopsy procedure, which was the source of tissue in the ovarian and lung cancer studies, heregulin mRNA was measured by RNA in situ hybridization (RNA-ISH). This is an assay in which a section of tissue is stained for heregulin mRNA and scored by a certified pathologist, and we are using a qualified version of this assay in our Phase 2 non-small cell lung cancer clinical trial.

**MM-141**

***MM-141 overview***

MM-141 is a fully human tetravalent bispecific antibody designed to block tumor survival signals by targeting receptor complexes containing the insulin-like growth factor 1 receptor, or IGF-1R, and ErbB3 (HER3) cell surface receptors. A tetravalent bispecific antibody is a single molecule that has four binding sites, two for each of two different target cell surface receptors. IGF-1R and ErbB3 complexes both activate a major signaling pathway, PI3K/AKT/mTOR, that allows tumor cells to grow and develop resistance to chemotherapy. We designed MM-141 to suppress the PI3K/AKT/mTOR signaling pathway by reducing the levels of IGF-1R and ErbB3 receptor complexes that trigger the pathway. MM-141 is currently being tested in a Phase 2 clinical trial in combination with gemcitabine and nab-paclitaxel in front-line metastatic pancreatic cancer. In 2014, we obtained orphan drug designation in the United States for MM-141 for the treatment of pancreatic cancer.

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***MM-141 Phase 2 clinical trial in metastatic pancreatic cancer***

In May 2015, we initiated a randomized, double-blinded, placebo-controlled Phase 2 clinical trial of MM-141 in combination with nab-paclitaxel and gemcitabine, versus nab-paclitaxel and gemcitabine alone in patients with newly diagnosed metastatic pancreatic cancer who have high serum levels of free IGF-1. As part of this trial, we expect that 146 front-line metastatic pancreatic cancer patients with high serum levels of free IGF-1 will be randomized (1:1) to receive either MM-141 plus nab-paclitaxel/gemcitabine or nab-paclitaxel/gemcitabine alone. Eligible patients for the trial must have received no prior radiotherapy, surgery, chemotherapy or investigational therapy for the treatment of metastatic disease. The primary endpoint of the trial is PFS. Secondary endpoints include overall survival, objective response rate, safety and tolerability.

***MM-141 Phase 1 clinical trial***

The design of our Phase 2 clinical trial of MM-141 was informed by our multi-arm Phase 1 clinical trial evaluating the safety and tolerability of MM-141 as a monotherapy and in combination with everolimus or with nab-paclitaxel and gemcitabine in patients with advanced solid tumors. Patients in the Phase 1 trial were enrolled in one of three arms: MM-141 as a monotherapy, MM-141 in combination with everolimus and MM-141 in combination with nab-paclitaxel and gemcitabine. Trial data showed common co-expression of IGF-1R and ErbB3 in solid tumors, and that the presence of this co-expression in metastatic pancreatic cancer was associated with decreased patient survival. An analysis of pre- and post-treatment biopsies confirmed that levels of IGF-1R and ErbB3 were decreased following MM-141 administration. Hyperglycemia was rare and was reported as an adverse event of Grade 3 or higher in one out of 38 patients in the trial (2.6%). The most common adverse events in the trial, of any grade, were nausea (50%), headache (47.4%) and vomiting (44.7%). MM-141 monotherapy was well tolerated with no dose limiting toxicities. The observed safety profile of MM-141 in combination with nab-paclitaxel and gemcitabine was comparable to expected toxicities reported with the individual safety profiles of the chemotherapy agents.

***MM-141 diagnostic development***

We are conducting research and development on an *in vitro* diagnostic for MM-141 that will help to determine which patients will derive benefits from the drug alone or in combination with other therapies, while experiencing a satisfactory safety profile. This research is focused on identifying pathway-relevant biomarkers and assessing their correlation with the magnitude of patient response to MM-141. Our Phase 2 clinical trial of MM-141 uses a proprietary, validated test to prospectively select patients with high serum-free IGF-1 levels for inclusion in the trial.

**MM-151**

***MM-151 overview***

MM-151 is an oligoclonal therapeutic consisting of a mixture of three fully human monoclonal antibodies designed to bind to non-overlapping epitopes of EGFR (ErbB1). An oligoclonal therapeutic is a mixture of two or more distinct monoclonal antibodies. EGFR (ErbB1) has long been recognized as an important drug target in several malignancies, including lung, breast, colon, pancreatic and head and neck cancers. MM-151 is designed to block the signal amplification that our research suggests occurs in the EGFR (ErbB1) pathway. We have completed a Phase 1 clinical trial of MM-151 in patients with refractory solid tumors.

We believe that there may be the potential to expand MM-151 into indications in which targeted EGFR (ErbB1) therapies are not currently approved, but which our preclinical research indicates should contain patients who will respond to these therapies. Potential indications include colorectal cancer, lung cancer and triple negative breast

cancer.

***MM-151 Phase 1 clinical trial***

We recently completed a Phase 1 clinical trial of MM-151 as a monotherapy and in combination with irinotecan in patients with solid tumors. The Phase 1 clinical trial was designed to assess the safety of MM-151 and determine the recommended Phase 2 dose. Four sites are participating in this trial.

***MM-151 diagnostic development***

We are focusing our diagnostic efforts for MM-151 on the identification of key biomarkers that will indicate which patient populations are likely to benefit from MM-151 treatment.

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**Combination Therapies**

In addition to the development described above, we are exploring combinations of our existing therapeutics that our systems biology approach suggests may be clinically relevant.

**Preclinical Product Candidates**

We are developing our preclinical product candidates for a range of solid tumor indications. Our most advanced preclinical candidates are MM-310, a targeted nanotherapeutic, and MM-131, a multispecific antibody.

**Our Approach to Cancer Research**

We view cancer as a complex engineering challenge. Through systems biology, which brings together the fields of biology, computing and engineering, we aim to decrease uncertainty in drug development and clinical validation, and move discovery efforts beyond trial and error. The goal of our systems biology approach is to understand how the complex molecular interactions that occur within cell signaling pathways, or networks, regulate cell decisions and how network dysfunction leads to disease. Our platform utilizes proprietary, dynamic biological data generated in a high-throughput method in which we test multiple biological or chemical parameters using engineering, analytical and modeling expertise, and from which we build computational models of cell biology to further our drug discovery, design and predictive development. We have developed an expertise in generating kinetic data, describing molecular changes or interactions over time, to illuminate the dynamic interactions that occur within biological systems, and apply our insights throughout the research and development process, including for target identification, lead compound design and optimization, diagnostic discovery and the design of clinical trial protocols.

Our models are constructed and validated using internally generated and proprietary data sets. Following the validation of a comprehensive model of a cell signaling network, we are able to use the model for drug discovery. Contrary to traditional methods, a significant portion of our discovery work takes place *in silico*, or using the model for simulation. We believe that this approach is more efficient and productive for drug discovery and development than traditional approaches.

As one example, we identified ErbB3, the target of MM-121, using our proprietary model of the ErbB signaling network after conducting a sensitivity analysis on its signaling process. Although the ErbB pathway has been extensively targeted by cancer therapeutics, we believe that understanding the relative importance of the different components of the ErbB network is central to identifying an attractive drug target and a therapeutic directed at this target. In this case, we built a computational model of the ErbB signaling network that includes the most potent ErbB receptor ligands, as well as known and novel ErbB inhibitors. We populated the model with proprietary dynamic data that we generated from our experiments. The model describes in mathematical equations 700 biochemical reactions representing the ErbB signal transduction network, and identified ErbB3 as the key node in response to both ErbB3- and EGFR (ErbB1)-binding ligands. We then used this insight to develop MM-121.

Ultimately, we believe that systems biology will result in better treatments for complex diseases by providing broader insight into disease and the potential therapeutic alternatives for physicians and patients. Using systems biology, we are incorporating the identification of biomarkers and the development of diagnostics into the drug development process. We believe that integrated medicines may enable physicians to deliver the right drug to the right set of patients at the right time. This may improve patient outcomes by providing improved therapeutics along with the diagnostic information to guide physician treatment decisions, reduce the overall costs of treating and caring for cancer patients, and provide a basis for seeking favorable reimbursement of approved drugs from payors because of the benefits to patients.

In addition to improving patient care, we believe that systems biology can increase the productivity of biomedical research, increase the probability of approval for new drugs and produce more precisely targeted therapeutics as compared to a conventional drug development approach since systems biology provides us with:

- a multidisciplinary, integrated approach to understanding complex biology;
- simulation and modeling capabilities that aid in the efficiency and productivity of development; and
- the capability to design and build a broad range of therapeutic product candidates without being limited to a particular drug design technology or target class.

Although our initial focus is oncology, we believe that our systems biology approach is applicable to a broad range of therapeutic areas beyond cancer, including bone and joint conditions, infectious disease, inflammation, central nervous system disease and other areas of medicine with high unmet needs. While it is possible that we may pursue some of these disease areas directly

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ourselves, our plan is to pursue many or all of these other areas through collaborations, licenses and other arrangements with third parties. As an example, in 2010, we established Silver Creek Pharmaceuticals, Inc., or Silver Creek, to apply our systems biology approach to the research and development of regenerative medicines to repair the heart. Silver Creek is currently a majority owned subsidiary.

***Therapeutic Design Capabilities***

We believe that the best therapies for the oncology indications that we are pursuing are targeted therapies that, in contrast with conventional chemotherapies, are highly selective for the molecular mechanisms that we are seeking to affect and, as a result, offer the potential for significant efficacy and safety benefits. Two such therapeutic approaches are our nanotherapeutics platform and our human antibody platform.

*Nanotherapeutics*

Our nanotherapeutics platform enables us to create both passively targeted and actively targeted liposomes, each containing different chemotherapeutic agents. Our nanotherapeutics are lipidic particles constructed to encapsulate active drug payloads. Nanoscale objects typically, though not exclusively, have dimensions on the order of 100 nanometers or smaller. We believe that nanotherapeutics offer the following potentially favorable attributes:

- The uniform sizing of our nanotherapeutics is intended to enable targeting and preferential deposition within tumors by taking advantage of the enhanced permeability and retention effect to selectively enter, and subsequently accumulate in, tumors with leaky vasculature.

- We formulate our nanotherapeutics to minimize the leakage of active drug payload out of the particle before the nanotherapeutic has reached the tumor, with the goal of limiting systemic exposure, and the associated occurrence of adverse events, and maximizing the amount of active drug that reaches the target.

- Encapsulation is designed to protect the active drug payload as it passes through the circulation and organs of the body, such as the liver, preventing premature clearance or metabolism of the active drug, and thereby extend the pharmacokinetic profile and enable more convenient dosing regimens.

- We can efficiently create targeted nanotherapeutics using our technical expertise and know-how that enable insertion of targeting agents, such as antibodies, into our nanotherapeutics.

- We can customize our nanotherapeutics for use with a variety of drug payloads, including chemotherapies, cytotoxics and nucleic acids, such as siRNA and genes.

*Human monoclonal antibodies*

Human antibodies are a key component of many of our targeted therapies based on their range of favorable attributes, including their significant target specificity and avidity relative to small molecules and their well understood pharmacokinetic properties. Our human monoclonal antibody engineering platform provides us with the ability to create antibodies that are designed to inhibit specific nodes responsible for tumor growth and survival, or to address

inherent drug resistance by simultaneously targeting redundant signaling pathways. We have designed antibodies for use as stand-alone therapeutics and have incorporated antibodies into other therapeutics, such as targeted nanotherapeutics, as targeting or docking agents. We work with several antibody formats, including the following:

Fully human recombinant monoclonal antibodies and fragments of fully human recombinant monoclonal antibodies that include the antibody binding domain. Monoclonal antibodies and antibody fragments are proteins that bind specifically to one defined site on a cell surface protein or receptor.

Multispecific antibody formats, which are comprised of two or more antibodies or antibody fragments linked to a common scaffold molecule to produce a single molecule that specifically binds to distinct epitopes on two or more target cell surface proteins or receptors.

Oligoclonal antibody mixtures, which are comprised of defined ratios of two or more recombinant human monoclonal antibodies that target two or more distinct epitopes on a single cell surface protein or receptor.

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**Manufacturing**

We manufacture bulk drug product for commercial use and for use in our clinical trials and research and development efforts using current good manufacturing practices, or cGMP, at our approximately 13,500 square foot multi-product facility located at our corporate headquarters in Cambridge, Massachusetts. We have the capabilities to manufacture antibodies, nanotherapeutics and antibody-targeted nanotherapeutics.

Our manufacturing capabilities encompass the full manufacturing process through quality control and quality assurance and are integrated with our project teams from discovery through development. This structure enables us to efficiently transfer research stage lead molecules into manufacturing. We have designed our manufacturing facility and processes to provide maximum flexibility and rapid changeover for the manufacture of different product candidates. We outsource fill-finish, packaging, labeling and distribution. As of January 31, 2016, we employed approximately 129 employees in manufacturing activities. Our facilities consist of two suites, one for nanoliposome manufacture and one for biologics manufacture.

Our nanoliposome suite is comprised of multiple classified clean rooms and has been designed to comply with current FDA and EMA cGMP for the manufacture of clinical and commercial bulk drug product. The facility and processes have been designed to meet the global commercial and clinical needs of ONIVYDE and the other nanoliposomal products in our pipeline. In 2015, the FDA audited and approved our nanoliposome suite for the commercial supply of bulk drug product for ONIVYDE, and in 2016, following inspection, the EMA found us to be in general compliance with the relevant EU manufacturing directives.

Our biologic suite produces our antibody product candidates and is comprised of multiple independent clean rooms, includes single-use bioreactors, and is sized to be able to produce sufficient material to meet the demands of our planned and ongoing clinical trials. We currently intend to continue to manufacture our bulk antibody product candidates at our current facility, except for MM-121 which is manufactured by a contract manufacturing organization, or CMO.

We believe that our strategic investment in manufacturing capabilities allows us to advance our product candidates more quickly and flexibly than would be possible at a CMO and produce drug substance in a cost-effective manner while retaining control over the process and timing. Nonetheless, we may utilize CMOs for our various manufacturing needs as we deem appropriate to meet our operational objectives.

We are developing and testing diagnostic assays for predictive biomarkers in an internal laboratory under Good Clinical Laboratory Practices and through collaborations with third-party vendors. Upon completion of the development of the diagnostic tests, we plan to evaluate external as well as internal options for manufacturing and commercialization of the tests.

We are leveraging our manufacturing capabilities to manufacture drug product on behalf of a third-party pharmaceutical company, and may enter into additional agreements to do so in the future. In 2013, we entered into an agreement with Watson Laboratories, Inc., or Actavis, as more fully described below, pursuant to which we will utilize our nanoliposomal manufacturing capabilities to develop, manufacture and exclusively supply the bulk form of doxorubicin HCl liposome injection to Actavis. Under this agreement, we have also agreed to develop additional products for Actavis, the identities of which will be mutually agreed upon in the future.

**Commercial Activities**

In October 2015, following receipt from the FDA of marketing approval for ONIVYDE, we commenced ONIVYDE commercial activities in the United States through our focused field organization. Prior to commercial launch, we spent time and resources building our marketing, field, access and distribution teams to provide healthcare education and reimbursement support as well as our product distribution infrastructure. We expect that our commercial infrastructure, which is currently supporting ONIVYDE, will form the basis of the organization that we would use to commercially support our other products, subject to receiving marketing approval for those other products. We believe that our commercial infrastructure provides the foundation to address the educational and supportive needs of oncologists who treat a broad array of tumor types, including lung, breast, ovarian, pancreatic, colorectal and gastric cancers. Outside the United States, we expect to either enter into distribution and other marketing arrangements with third parties for any of our other product candidates that obtain marketing approval, or we may expand our commercial organization to support such territories ourselves.

We plan to tightly integrate the marketing of our therapeutics and diagnostics, subject to receipt of marketing approval for any such future products beyond ONIVYDE. As we expect to pair various types of diagnostics with our therapeutics, it is likely that the commercialization strategy and business model employed for our various diagnostics may differ from one another.

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Outside of the United States and Taiwan, Baxalta has exclusive commercialization rights for all potential indications of ONIVYDE worldwide. PharmaEngine has exclusive commercialization rights in Taiwan. We believe our commercialization partners for ONIVYDE possess the relevant expertise to successfully commercialize ONIVYDE outside of the United States. For instance, Baxalta has previously demonstrated the ability to successfully launch innovative products, penetrate markets and drive the growth of multiple brands in highly competitive markets.

**Competition**

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

Many of our competitors may 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. Mergers and acquisitions in the pharmaceutical, biotechnology and diagnostic industries may result in even more resources being concentrated among a smaller number of our competitors. 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. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

The key competitive factors affecting the success of all of our product candidates, if approved, are likely to be their efficacy, safety, convenience, price, the effectiveness of diagnostics in guiding the use of related therapeutics, the level of generic competition and the availability of reimbursement from government and other third-party payors.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours. In addition, our ability to compete may be affected because in many cases insurers or other third-party payors seek to encourage the use of generic products. There are many generic products currently on the market for the indications that we are pursuing, and additional products are expected to become available on a generic basis over the coming years. If our therapeutic product candidates are approved, we expect that they will be priced at a significant premium over competitive generic products.

The initial focus of our business is to develop therapeutics and diagnostics for the treatment of solid tumor cancers. Cancer is the second most common cause of death in the United States, exceeded only by heart disease, and accounts for almost one of every four deaths in the United States. There are a variety of available drug therapies marketed for solid tumors. In many cases, these drugs are administered in combination to enhance efficacy. Some of these drugs are branded and subject to patent protection, and others are available on a generic basis, including the active ingredients in ONIVYDE and MM-302. Many of these approved drugs are well established therapies and are widely accepted by physicians, patients and third-party payors. In general, although there has been considerable progress over the past few decades in the treatment of solid tumors and the currently marketed therapies provide benefits to many patients, these therapies all are limited to some extent in their efficacy and frequency of adverse events, and none of them are successful in treating all patients. As a result, the level of morbidity and mortality from solid tumor cancers remains

high.

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The following table sets forth information about the incidence and selected treatments for some of the solid tumor cancers for which we have developed and are developing therapeutic product candidates and diagnostics. The U.S. estimated annual incidence is based on information from the American Cancer Society, *Cancer Fact & Figures 2016*.

| Tumor Type | U.S. Annual Incidence | Selected Marketed Therapies |
|---|---|---|
| Breast | 249,260 | trastuzumab (Herceptin®); docetaxel (Taxotere®); paclitaxel (Taxol®, Abraxane®); capecitabine (Xeloda®); tamoxifen (Nolvadex®, Soltamox®); anastrazole (Arimidex®); letrozole (Femara®); exemestane (Aromasin®); ado-trastuzumab emtansine (Kadcyla®); pertuzumab (Perjeta®); everolimus (Afinitor®); palbociclib (Ibrance®) |
| Lung and bronchus | 224,390 | ceritinib (Zykadia®); crizotinib (Xalkori®); docetaxel (Taxotere); gemcitabine (Gemzar®); pemetrexed (Alimta®); gefitinib (Iressa®); erlotinib (Tarceva®); bevacizumab (Avastin®); paclitaxel (Taxol, Abraxane); nivolumab (Opdivo®); pembrolizumab (Keytruda®) |
| Colorectal | 134,490 | oxaliplatin (Eloxatin®); irinotecan (Camptosar®); bevacizumab (Avastin); cetuximab (Erbitux®); panitumumab (Vectibix®); ziv-aflibercept (Zaltrap®); trifluridine/tipiracil (Lonsurf®); regorafenib (Stivarga®) |
| Pancreatic | 53,070 | nab-paclitaxel (Abraxane); gemcitabine (Gemzar); erlotinib (Tarceva) |
| Liver | 39,230 | sorafenib (Nexavar®) |
| Brain and other nervous system cancers | 23,770 | temozolomide (Temodar®); carmustine (BiCNU®); polifeprosan 20 with carmustine implant (Gliadel®); bevacizumab (Avastin) |
| Gastric | 26,370 | ramucirumab (Cyramza®); capecitabine (Xeloda); trastuzumab (Herceptin); docetaxel (Taxotere); oxaliplatin (Eloxatin); epirubicin (Ellence®) |
| Ovarian | 22,280 | olaparib (Lynparza®); liposomal doxorubicin (Doxil®); bevacizumab (Avastin); paclitaxel (Taxol, Abraxane); gemcitabine (Gemzar) |

In addition to the marketed and generic therapies for solid tumors, there are also a number of products in late stage clinical development to treat solid tumors. These products in development may provide efficacy, safety, convenience and other benefits that are not provided by currently marketed therapies. As a result, they may provide significant competition for any of our product candidates for which we obtain market approval.

***Pancreatic Cancer***

The only indication in the United States for which we have received marketing approval from the FDA is for ONIVYDE in combination with 5-FU and leucovorin for the treatment of patients with metastatic adenocarcinoma of

the pancreas after disease progression following gemcitabine-based therapy. Pancreatic cancer is a rare and deadly disease. There are approximately 53,000 patients diagnosed with pancreatic cancer each year in the United States, the overwhelming majority of whom have adenocarcinoma. Globally there are approximately 338,000 new cases each year. Most patients receive gemcitabine-based therapy during either adjuvant/neoadjuvant treatment for locally advanced disease or during first- or second-line therapy for metastatic disease.

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**Collaboration and License Agreements**

We are party to a number of collaboration agreements for the development and commercialization of our product candidates and license agreements under which we license patents, patent applications and other intellectual property. We consider the following collaboration and license agreements to be material to our business.

***Baxalta***

On September 23, 2014, we entered into a license and collaboration agreement with Baxter International Inc., Baxter Healthcare Corporation and Baxter Healthcare SA, or the Baxalta agreement, for the development and commercialization of ONIVYDE outside of the United States and Taiwan, or the licensed territory. In connection with Baxter International Inc. s separation of the Baxalta business, the Baxalta agreement was assigned to Baxalta during the second quarter of 2015. As part of the Baxalta agreement, we granted Baxalta an exclusive, royalty-bearing right and license under our patent rights and know-how to develop and commercialize ONIVYDE in the licensed territory. Baxalta is responsible for using commercially reasonable efforts to develop, obtain regulatory approvals for and, following regulatory approval, commercialize ONIVYDE in the licensed territory. A joint steering committee comprised of an equal number of representatives from each of Baxalta and us is responsible for approving changes to the global development plan for ONIVYDE, including all budgets, and overseeing the parties development and commercialization activities with respect to ONIVYDE. Unless otherwise agreed, we will be responsible for conducting all clinical trials contemplated by the global development plan for ONIVYDE and manufacturing all clinical material needed for such trials.

Under the terms of the Baxalta agreement, we received a $100.0 million upfront, nonrefundable cash payment in September 2014. In addition, we are eligible to receive from Baxalta (i) up to an aggregate of $100.0 million upon the achievement of specified research and development milestones, of which we have received $62.5 million from Baxalta as of December 31, 2015, (ii) up to an aggregate of $520.0 million upon the achievement of specified regulatory milestones, of which we have received $20.0 million from Baxalta as of December 31, 2015, and (iii) up to an aggregate of $250.0 million upon the achievement of specified sales milestones. Under the terms of the Baxalta agreement, we will bear up to the first $98.8 million of costs related to the development of ONIVYDE for pancreatic cancer patients who have not previously received gemcitabine-based therapy; however, we expect most of these costs to be offset by payments received upon the achievement of clinical trial-related milestones. We will share equally with Baxalta all other clinical trial costs contemplated by the global development plan. We are also entitled to tiered, escalating royalties ranging from sub-teen double-digits to low twenties percentages of net sales of ONIVYDE in the licensed territory.

We expect to enter into a commercial supply agreement with Baxalta pursuant to which we will supply ONIVYDE bulk drug substance to Baxalta and, at Baxalta s option, may manage fill and finish activities to be conducted by a third-party contract manufacturer for Baxalta. Baxalta also has the option to manufacture ONIVYDE itself, in which case we will perform a technology transfer of our manufacturing process to Baxalta.

If not terminated earlier by either party, the Baxalta agreement will expire upon expiration of all royalty and other payment obligations of Baxalta under the Baxalta agreement. Either party may terminate the Baxalta agreement in the event of an uncured material breach by the other party. Baxalta may also terminate the Baxalta agreement on a product-by-product, country-by-country or sub-territory-by-sub-territory basis or in its entirety, for its convenience, upon 180 days prior written notice. In addition, we may terminate the Baxalta agreement if Baxalta challenges or supports any challenge of our licensed patent rights.

Under the Baxalta agreement, Baxalta has also agreed that, subject to limited exceptions, until September 23, 2017, neither Baxalta nor any of its affiliates will (1) effect or seek, offer or propose to effect, or cause or participate in or in any way advise, assist or encourage any other person to effect or seek, offer or propose to effect or cause or participate in, any acquisition of any of our securities or assets, any tender or exchange offer, merger or other business combination involving us, any recapitalization, restructuring, liquidation, dissolution or other extraordinary transaction with respect to us, or any solicitation of proxies or consents to vote any of our voting securities, (2) form, join or in any way participate in a group with respect to any of our securities, (3) otherwise act, alone or in concert with others, to seek to control or influence our management, board of directors or policies, (4) take any action that might force us to make a public announcement regarding any of the foregoing or (5) enter into any agreements, discussions or arrangements with any third party with respect to any of the foregoing.

***PharmaEngine***

In May 2011, we entered into an assignment, sublicense and collaboration agreement with PharmaEngine, or the PharmaEngine agreement. Under the agreement, PharmaEngine assigned to us its rights and obligations under a 2005 agreement with Hermes BioSciences, Inc., or Hermes, to develop and commercialize MM-398 in Europe and certain countries in Asia. Through our acquisition of Hermes in 2009, we held the rights to MM-398 in North America and the rest of the world. PharmaEngine also granted to us an exclusive right and license, with the right to sublicense, under PharmaEngine technology and rights to develop and

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commercialize MM-398 worldwide outside of Taiwan. We granted to PharmaEngine a paid-up, royalty free, exclusive right and license under our technology and rights to develop and commercialize MM-398 in Taiwan. Upon entering into the PharmaEngine agreement, we paid PharmaEngine a $10.0 million upfront license fee. In addition, we made a milestone payment of $5.0 million to PharmaEngine in connection with dosing the first patient in our Phase 3 clinical trial of MM-398, which occurred and was paid in the first quarter of 2012.

In September 2014, we amended the PharmaEngine agreement to redefine sublicense revenue and reduce the portion of sublicense revenue that we are required to pay to PharmaEngine. As a result of this amendment, we made a $7.0 million milestone payment to PharmaEngine in September 2014. Additionally, as a result of this amendment, a previously contingent $5.0 million milestone payment was paid to PharmaEngine in the second quarter of 2015. Prior to the amendment of the PharmaEngine agreement, this milestone payment was contingent upon the award of certain specified regulatory designations. In July 2015, we made an $11.0 million milestone payment to PharmaEngine in connection with the EMA s acceptance for review of an MAA for MM-398.

Since entering into the PharmaEngine agreement, we have paid PharmaEngine an aggregate of $38.0 million in upfront license fees and milestone payments. In addition to these amounts, we could also be required to pay PharmaEngine up to an additional $60.0 million in aggregate regulatory milestones, $38.5 million in sublicense fees and $130.0 million in aggregate sales milestones, in each case with respect to Europe and certain countries in Asia. Under the agreement, PharmaEngine is entitled to tiered royalties based on net sales of MM-398 in Europe and certain countries in Asia. The royalty rates under the agreement range from high single digits up to the low teens as a percentage of our net sales of MM-398 in these territories. Our obligation to pay royalties to PharmaEngine continues on a country-by-country basis until ten years after the first commercial sale of MM-398 in such country. We are responsible for the development and commercialization, and all related costs and expenses, of MM-398 in all countries except Taiwan, where PharmaEngine retains the right to develop and commercialize MM-398 at its expense. Each party has agreed to use commercially reasonable efforts to develop, in accordance with a development plan, and commercialize MM-398 in its respective territory.

Multiple executive committees were formed under the PharmaEngine agreement, each comprised of an equal number of representatives from each party. The steering committee is responsible for reviewing and approving changes to the development plan, providing overall strategic direction with respect to development of MM-398 under the development plan and overseeing other committees. The steering committee is also responsible for resolving any disputes arising under the agreement at the steering committee or that are referred to it by any of the other committees. If a matter is unresolved by the steering committee, it may be referred for resolution to executive officers from both companies. We have final decision making authority on any such matter not resolved by the executive officers that relates to the worldwide development of MM-398 or commercialization of MM-398 outside of Taiwan. The development committee is responsible for recommending to the steering committee changes to the development plan and overseeing the progress of the development program and monitoring the parties compliance with their respective obligations under the development plan.

Upon expiration of all royalty and other payment obligations due to PharmaEngine under this agreement on a country-by-country basis, the licenses granted under the agreement will be deemed to be perpetual, fully paid-up and irrevocable with respect to the licensed product in such country. Either party may terminate the agreement in the event of an uncured material breach by the other party. In addition, we may terminate the agreement for convenience upon 90 days prior written notice. If PharmaEngine terminates this agreement in its entirety or with respect to Europe or the Asian territories because of our material breach, or if we terminate the agreement for convenience with respect to Europe or the Asian territories, then we are required to grant PharmaEngine a license under our technology and rights with respect to MM-398 in Europe or the Asian territories, as applicable, and PharmaEngine is required to pay us single-digit royalties for net sales of MM-398 in such territories.

***Actavis***

In November 2013, we entered into a development, license and supply agreement with Actavis, or the Actavis agreement, pursuant to which we will develop, manufacture and exclusively supply the bulk form of doxorubicin HCl liposome injection, or the initial product, to Actavis. The Actavis agreement was subsequently amended in January 2015 to transfer certain responsibilities from us to Actavis in exchange for reducing the aggregate milestone payments that we are eligible to receive by $0.4 million. Under the Actavis agreement, Actavis is responsible for all costs related to finished product processing and global commercialization. Pursuant to the Actavis agreement, we have also agreed to develop additional products for Actavis in the future, the identities of which will be mutually agreed upon. We are eligible to receive up to $15.1 million under the Actavis agreement, of which $3.9 million has been received through December 31, 2015, and the remainder is expected to be received in development funding and development, regulatory and commercial milestone payments related to the initial product. We will also receive a double digit percentage of net profits on global sales of the initial product and any additional products. We will manufacture and supply the initial product to Actavis in bulk form at an agreed upon unit price.

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The Actavis agreement will expire with respect to the initial product and any additional products developed in the future ten years after Actavis first sale of the applicable product, unless terminated earlier, and will automatically renew for additional two year periods thereafter unless either party provides notice of non-renewal. Either party may terminate the Actavis agreement in the event of an uncured material breach or bankruptcy filing by the other party. Actavis may also terminate the agreement for convenience in specified circumstances upon 90 days prior written notice.

***Dyax***

In January 2007, we entered into an amended and restated collaboration agreement with Dyax Corp., or Dyax, which superseded a prior collaboration agreement with Dyax that we entered into in December 2005. Under this collaboration agreement, Dyax uses its proprietary phage display technology to identify antibodies that bind to targets of interest to us as therapeutics or diagnostics. Further, Dyax has granted to us a worldwide, non-exclusive, royalty free right to use and make any and all of the antibodies identified by Dyax for certain research purposes. In order to clinically develop or commercialize any such antibody, however, we must obtain an additional product license from Dyax on a target-by-target basis. We have the option to obtain one or more product licenses on terms set forth in the collaboration agreement, subject to limitations on the availability of each such product license under an agreement between Dyax and Cambridge Antibody Technologies, which has merged with MedImmune, LLC and is now owned by AstraZeneca PLC. In January 2016, Dyax was acquired by Shire plc.

As consideration for the grant of the initial research license, we paid Dyax a research fee based on the total estimated full time equivalent researchers that were required to conduct the research plan and a fee for achieving certain technical milestones. If we elect to obtain a product license with respect to any therapeutic or diagnostic target, we are required to pay to Dyax an additional upfront license fee for the applicable antibody. We also may be required to make additional maximum aggregate development and regulatory milestone payments of $16.2 million for therapeutic products and maximum aggregate regulatory milestone payments of $1.0 million for diagnostic products directed to selected targets. In addition, Dyax is entitled to mid single digit royalties based on net sales of products covered by any product license that we obtain from Dyax. Our obligation to pay royalties to Dyax continues on a product-by-product and country-by-country basis until the later of a specified number of years after the first commercial sale of the product in such country and the expiration of the patent rights covering the product in such country. MM-121 and a component of MM-141 were identified under this agreement, and we have obtained the required target licenses from Dyax by exercising our product license options and paying the applicable license fees. We are obligated to use commercially reasonable efforts to develop and commercialize the antibodies for which we obtain a commercial license.

This agreement will remain in effect, unless terminated earlier, for so long as we or any of our affiliates or sublicensees continue to develop or commercialize products that remain royalty-bearing under the agreement. Either party may terminate the agreement in the event of an uncured material breach by the other party. We also may terminate the agreement in its entirety or on a product-by-product basis at any time upon 90 days prior written notice.

***Adimab***

In November 2009, we entered into a collaboration agreement with Adimab LLC, or Adimab, to allow us to evaluate the utility of using antibodies identified during the collaboration as therapeutics or diagnostics. Under the agreement, Adimab granted to us a worldwide, non-exclusive, royalty free right to use materials provided by Adimab to perform non-clinical research during the evaluation term. Adimab also granted to us an option to obtain the assignment of specified patent rights claiming the selected antibodies and a license under Adimab s background patent rights and know-how for the development and commercialization of the antibodies.

As partial consideration for the research license grant, we paid Adimab a technology access fee at the time of grant, research fees based on the total estimated full time equivalent researchers that were required to conduct the research plan and a fee for achieving certain technical milestones. We have exercised our assignment and license option by paying Adimab a fee of $1.0 million. In addition, we are required to pay Adimab up to an aggregate of $13.5 million per therapeutic area, for the first four therapeutic areas, upon achievement of specified development and regulatory milestones, of which we have paid $1.5 million with respect to the first therapeutic area, and up to an aggregate of $500,000 per diagnostic product upon the achievement of specified regulatory milestones. In addition, Adimab is entitled to mid single digit royalty payments based on net sales of therapeutic products and diagnostic products arising from the collaboration. Our obligation to pay royalties to Adimab continues on a product-by-product and country-by-country basis until the later of a specified number of years after the first commercial sale of the product in such country and the expiration of the patent rights covering the product in such country, provided that the royalty term will not extend beyond a specified number of years after the first commercial sale of the product in such country. We are obligated to use commercially reasonable efforts to develop and commercialize at least one product that incorporates the antibodies for which we exercised our assignment and license option in each of the United States, Europe and Japan. MM-151 was generated under this agreement.

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The term of the agreement expires on a country-by-country basis on the earliest date after which no payments are due to Adimab, unless earlier terminated. Either party may terminate the agreement in the event of an uncured material breach by the other party. In addition, we may terminate the agreement at any time upon 90 days prior written notice.

***University of California***

In November 2000, we entered into a separate exclusive license agreement with The Regents of the University of California, or the Regents. Under the agreement, the Regents granted us a royalty-bearing world-wide right and license under certain patent rights for the development and commercialization of products that are covered by the licensed patent rights, including MM-302. The agreement requires that we diligently pursue the development, manufacture and commercialization of licensed products. In addition, we are required to meet specified development, regulatory and commercialization milestones within timeframes specified in the agreement. We have the sole responsibility for the development and commercialization of products under the licensed technology.

We are required to pay to the Regents an annual license maintenance fee of $95,000 until the first commercial sale of a licensed product. We also are responsible for all development costs and have agreed to spend a minimum of $150,000 per year for such costs. In addition, we are responsible for up to an aggregate of $700,000 per product upon the achievement of specified development and regulatory milestones. The Regents are also entitled to royalties in the low single digits based on net sales of products covered by the licensed technology. If we sublicense the rights granted to us under the licensed technology to a third party, then we are also obligated to pay to the Regents a portion of the sublicensing income related to the licensed technology.

If not terminated earlier, this agreement terminates upon the expiration or abandonment of all patents licensed under this agreement. The Regents may terminate the agreement in the event of an uncured material breach by us. We may terminate the agreement on a country-by-country basis at any time upon 60 days prior written notice.

**Intellectual Property**

Our success will significantly depend on our ability to obtain and maintain patent and other proprietary protection for our commercially important technology, inventions and know-how, defend and enforce our patents, preserve the confidentiality of our trade secrets, establish and protect our commercial brands and operate without infringing the valid and enforceable patents and proprietary rights of third parties. To accomplish this, we rely on a combination of intellectual property rights, including patents, trade secrets, copyrights and trademarks, as well as regulatory exclusivity and contractual protections. We aggressively strive to protect the proprietary technology that we believe is important to our business, including seeking and maintaining patents intended to cover our products and compositions, their methods of use and processes for their manufacture, as well as our diagnostic and drug discovery technologies and any other inventions that are commercially important to the development of our business. In some circumstances, we also rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection, such as our proprietary network modeling programs and large scale protein and liposome production methods.

We also rely on trademark protection of our corporate and product brands. We are the owner of multiple federal trademark registrations in the United States and outside the United States. ONIVYDE® is a registered U.S. trademark of Merrimack Pharmaceuticals, Inc. In addition, we have multiple additional pending trademark registration applications in the United States and other countries covering the MERRIMACK™ and PROVYDE™ word marks and related logos in trademark classes relevant to our products and services.

We seek to protect our proprietary technology and processes, in part, by confidentiality agreements with our employees, consultants, scientific advisors and contractors. We require each of our employees, consultants and advisors to execute a confidentiality and inventions assignment agreement before beginning their employment, consulting or advisory relationship with us. These agreements generally provide that the individual must keep confidential and not disclose to other parties any confidential information developed or learned by the individual during the course of their relationship with us except in limited circumstances. These agreements also generally provide that we will own all inventions conceived by the individual in the course of rendering services to us. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our consultants, contractors or collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

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Our commercial success will depend in part on obtaining and maintaining patent protection and trade secret protection of the use, formulation, manufacture and composition of our products and product candidates, as well as successfully asserting and/or defending these patents against third-party challenges. Our ability to protect our products and product candidates from unauthorized making, using, selling, offering to sell or importing by third parties is dependent on the extent to which we have rights under valid and enforceable patents that cover these activities.

As of January 31, 2016, we owned or controlled a total of 21 issued U.S. patents and 119 corresponding issued foreign patents, in addition to 72 pending U.S. patent applications and 167 pending patent applications in the rest of the world, covering our most advanced product candidates. We intend to continue to protect our proprietary technology with additional filings as appropriate. We do not have patents or patent applications in every jurisdiction where there is a potential commercial market for our product candidates. We continually evaluate our patent portfolio and patent strategy and believe our owned and licensed patents and patent applications, as well as applicable periods of regulatory exclusivity available after new product approval, provide us with a competitive advantage; however, if markets where we do not have patents or patent applications become commercially important, our business may be adversely affected.

The latest patent expiration dates for issued patents covering the composition or use of each of our most advanced product candidates as of January 31, 2016 are summarized below. As described in more detail below, the expiration dates in the table below refer to the latest-expiring granted patent covering the product, product candidate, technology or use thereof in the United States, and one or more countries outside of the United States, but do not account for any patent term extension or extended exclusivity terms, such as pediatric extensions, that may be available in the United States and certain foreign jurisdictions.

| Product Candidate/Technology | Latest Year of Expiration of Current Patent Protection in the United States | Latest Year of Expiration of Current Patent Protection outside the United States |
|---|---|---|
| MM-398 | 2028 | 2025 |
| MM-302 | 2031 | 2019 |
| MM-121 | 2031 | 2031 |
| MM-141 | 2032 | 2032 |
| MM-151 | 2032 | 2032 |

The term of individual patents depends upon the legal term for patents in the countries in which they are obtained. In most countries, including the United States, the patent term is 20 years from the earliest filing date of a non-provisional patent application.

In the United States, a patent s term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier filed patent. In the future, if and when our product candidates receive approval by the FDA or foreign regulatory authorities, we expect to apply for patent term extensions on issued patents covering those products, depending upon the length of the clinical trials for each drug and other factors, including those involved in the filing of a new drug application, or NDA, or a biologics license application, or BLA. The Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, permits a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process, provided the total patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product s approval date. The patent term restoration period is generally calculated as one-half the time between the effective date of an investigational new drug

application, or IND, and the submission date of an NDA, plus the time between the submission date of an NDA and the FDA s approval of that application. Only one patent applicable to each approved drug is eligible for the extension and the application for extension must be made prior to expiration of the patent. The U.S. Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration.

Similar provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug. The stated patent exclusivity dates for patent exclusivity outside of the United States may also be eligible for further extension, and/or regulatory market and/or data exclusivity in certain countries, upon product approval in individual countries for various reasons, including supplemental protection certificate(s) after product approval in eligible countries outside the United States, and/or conducting certain investigations of pediatric exclusivity or use of products covered by the applicable patent.

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***ONIVYDE (MM-398)***

ONIVYDE (irinotecan liposome injection) is covered by issued U.S. patents on the product composition through at least 2028, and corresponding issued patents in other countries through at least 2025, not including additional exclusivity upon product approval from patent term extension, supplemental protection certificates and/or pediatric exclusivity.

In the United States, ONIVYDE is covered by multiple issued patents, including four U.S. patents listed in the FDA s Approved Drug Products with Therapeutic Equivalence Evaluations publication, commonly known as the Orange Book, covering the ONIVYDE drug product and drug substance (through at least 2028) or approved methods of using ONIVYDE (through at least 2025). We have applied for restoration of patent term, or patent term extension, for at least one of our U.S. ONIVYDE patents listed in the Orange Book, to add patent life beyond the current expiration date. In addition, ONIVYDE may be eligible to receive an additional six months of exclusivity added to the term of individual patents and any other marketing exclusivity covering ONIVYDE under the Best Pharmaceuticals for Children Act, or BPCA, if we were to submit information which could be requested in writing by the FDA relating to the use of the active moiety of the drug in children. We also own multiple pending patent applications covering the manufacture and use of ONIVYDE in various indications, including pancreatic cancer, through at least 2033, if issued.

Outside the United States, the ONIVYDE composition is covered by issued patents through 2025 in Japan and eight other countries, and pending patent applications with the European Patent Office and 13 additional countries. In addition, we own multiple pending patent applications that, if issued, provide additional patent coverage on the use of ONIVYDE for various indications, including pancreatic cancer, through at least 2033. We may apply for extended exclusivity terms (supplemental protection certificates) for our other patents world-wide as appropriate, depending on the expected length of clinical trials and other factors involved in the submission of the relevant drug approval application.

***MM-302***

We own patent coverage on the use of the MM-302 composition in treating various forms of cancer (including breast cancer) through at least 2031 in the United States. In addition, we have an exclusive license to patents covering the MM-302 composition through at least 2019 in the United States and Europe. Our patent coverage does not include additional exclusivity available after product approval from patent term extension, supplemental protection certificates and/or pediatric exclusivity. In addition, we own multiple pending patent applications in the United States, Europe and other countries covering various related methods of use (expiring between 2031 and 2035, if issued) and/or related diagnostic tests and methods (expiring between 2033 and 2034, if issued).

***MM-121 (seribantumab)***

We own issued patents in the United States, Europe, Japan and nine other countries covering the MM-121 composition through at least 2028, not including additional exclusivity available after product approval from patent term extension, supplemental protection certificates and/or pediatric exclusivity. In addition, we own multiple pending patent applications in the United States, Europe and other countries covering various related methods of use, including the treatment of patients with heregulin positive forms of cancer (through 2034, if issued), treatment of patients with certain forms of breast cancer (expiring between 2031 and 2032, if issued) and/or related diagnostic tests and methods (through 2029, if issued).

***MM-141 (istiratumab)***

We own issued patents in the United States and Japan, and pending patent applications in Europe and 10 other countries covering the MM-141 composition through at least 2032, not including additional exclusivity available after product approval from patent term extension, supplemental protection certificates and/or pediatric exclusivity. In addition, we own multiple pending patent applications in the United States and the Patent Cooperation Treaty, or PCT, covering methods of treating pancreatic cancer with MM-141 through 2035, if issued.

***MM-151***

We own issued patents in the United States, and pending patent applications in Europe, Japan and nine other countries covering the MM-151 composition and related patient diagnostic technology through at least 2032, not including additional exclusivity available after product approval from patent term extension, supplemental protection certificates and/or pediatric exclusivity. In addition, we own multiple pending patent applications in the United States and the PCT covering methods of treating colorectal cancer with MM-151 through 2035, if issued.

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**Silver Creek**

In August 2010, we acquired 12,000,000 shares of Series A preferred stock of Silver Creek in exchange for our grant to Silver Creek of technology licenses. We granted to Silver Creek a royalty free license under certain antibody growth factor patent rights to develop and commercialize products covered by the licensed patent rights. This license is exclusive to Silver Creek for therapeutic or diagnostic use in humans for the promotion of organ regeneration and co-exclusive with us for all other uses. We also granted to Silver Creek royalty free, non-exclusive licenses under certain patent rights and know-how to use certain of our technologies for research and development purposes. Either party may terminate the agreement in the event of an uncured material breach by the other party.

In August and December 2010, Silver Creek issued and sold an aggregate of 4,189,904 additional shares of its Series A preferred stock at a price per share of $1.00 to other investors for an aggregate purchase price of $4,189,904. In addition, on December 21, 2012, Silver Creek entered into a Note Purchase Agreement pursuant to which it issued convertible notes to various lenders, which did not include us, in aggregate principal amounts of $1.6 million in December 2012, $0.3 million in February 2013 and $0.6 million in December 2013. The convertible notes bore interest at 6%. The notes matured and converted, along with an immaterial amount of accrued interest, into 2,603,281 shares of Silver Creek Series A preferred stock on December 31, 2013. During the year ended December 31, 2014, Silver Creek issued convertible notes to various lenders, which did not include us, in aggregate principal amounts of an additional $1.0 million. The convertible notes bore interest at 6% and matured and converted, along with an immaterial amount of accrued interest, into approximately 1.0 million shares of Silver Creek Series A preferred stock on December 31, 2014. During the year ended December 31, 2015, Silver Creek issued and sold a total of 1.6 million shares of its Series B preferred stock at a price per share of $1.35 to investors and received net proceeds of $2.1 million, after deducting issuance costs. As of December 31, 2015 and 2014, we owned approximately 56% and 60%, respectively, of the outstanding capital stock of Silver Creek, making Silver Creek a majority owned subsidiary.

Silver Creek is applying our systems biology approach to the research and development of regenerative medicines to repair the heart. In the future, we may consider forming additional businesses or business units to apply our systems biology approach to multiple additional disease areas outside the oncology field. We expect to do so in some cases, as with Silver Creek, through the establishment of separately funded companies.

**Government Regulation**

Government authorities in the United States, at the federal, state and local level, and in other countries extensively regulate, among other things, the research, development, testing, manufacture, including any manufacturing changes, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, import and export of pharmaceutical products, biological products and medical devices, such as those we are developing.

***United States drug and biological product approval process***

In the United States, the FDA regulates drugs and biological products under the Federal Food, Drug, and Cosmetic Act, or FDCA, the Public Health Service Act, or PHSA, and implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable United States requirements at any time during the product development process, approval process or after approval may subject an applicant to a variety of administrative or judicial actions, including, among other things, the FDA s refusal to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of untitled or warning letters, product recalls, product seizures, total or partial suspension of production or distribution

injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, civil penalties and criminal prosecution.

Generally, the process required by the FDA before a drug or biological product may be marketed in the United States involves the following:

completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA s good laboratory practice, or GLP, regulations;

submission to the FDA of an IND, which must become effective before human clinical trials may begin;

approval by an independent institutional review board, or IRB, at each clinical site before each trial may be initiated;

performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug or biological product for each indication;

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submission to the FDA of an NDA or an abbreviated new drug application, or ANDA, for drug products or BLA for biological products, as applicable;

satisfactory completion of an FDA advisory committee review, if applicable;

satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with cGMP requirements and to assure that the facilities, methods and controls are adequate to preserve the drug s identity, strength, quality and purity; and

FDA review and approval of the NDA or BLA.

We expect that all of our clinical product candidates, other than ONIVYDE, will be subject to review as biological products under BLA standards. We expect that ONIVYDE will continue to be subject to review as a drug under NDA standards. MM-302 contains both drug and biological components. We believe that this combination product will be subject to review as a biological product, pursuant to a BLA.

*Preclinical studies*

Preclinical studies include laboratory evaluation of product chemistry and formulation, as well as *in vitro* and animal studies to assess the potential for adverse events and in some cases to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed protocol for clinical studies, among other things, to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, may continue after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the trial on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not necessarily result in the FDA allowing clinical trials to commence.

*Clinical trials*

Clinical trials involve the administration of the investigational new drug to human subjects healthy volunteers or patients under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, an IRB at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove the study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB may also require the clinical trial at the site to be halted, either temporarily or permanently, for failure to comply with the IRB s requirements, or may impose other conditions. For clinical trials involving an IND, an IRB must operate in compliance with FDA regulations. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health for public dissemination on their ClinicalTrials.gov website.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined:

*Phase 1:* The drug or biological product is initially introduced into healthy human subjects or patients with the target disease or condition and tested for safety, side effects associated with increasing doses, pharmacological action, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness.

*Phase 2:* The drug or biological product is administered to a limited patient population to identify common adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

*Phase 3:* The drug or biological product is administered to an expanded patient population in adequate and well-controlled clinical trials, typically at geographically dispersed clinical trial sites, to generate sufficient data to statistically confirm the efficacy and safety of the product for approval, to permit the FDA to evaluate the overall risk-benefit profile of the product and to provide adequate information for the labeling of the product.

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Progress reports detailing the results of clinical trials involving an IND must be submitted at least annually to the FDA and more frequently if serious adverse events occur. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB s requirements or if the drug or biologic product has been associated with unexpected serious harm to patients.

*Disclosure of clinical trial information*

Sponsors of applicable clinical trials of FDA regulated products, including drugs, are required to register and disclose certain clinical trial information. Information related to the product, patient population, phase of investigation, study sites and investigators, and other aspects of the clinical trial is then made public on the ClinicalTrials.gov website as part of the registration. Sponsors are also obligated to disclose the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed until the new product or new indication being studied has been approved. Competitors may use this publicly available information to gain knowledge regarding the progress of development programs.

*Marketing approval*

Assuming successful completion of the required clinical testing, the results of the preclinical and clinical studies, together with detailed information relating to the product s pharmacology chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA or BLA requesting approval to market the product for one or more indications. FDA approval of the NDA or BLA is required before marketing of the product may begin in the United States. Under federal law, the submission of most NDAs and BLAs is subject to a substantial application user fee, currently $2,374,200 for fiscal year 2016, and the sponsor of an approved NDA or BLA is also subject to annual product and establishment user fees, currently $114,450 per product and $585,200 per establishment. These fees are typically increased annually.

The FDA conducts a preliminary review of all NDAs and BLAs within the first 60 days after receipt before accepting them for filing based on the agency s threshold determination that they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA or BLA for filing. In this event, the application must be resubmitted with the additional information, which would also be 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. The FDA has agreed to specified performance goals in the review of NDAs and BLAs. Most such applications for non-priority products are reviewed within ten to twelve months after filing, and most applications for priority review products, that is, drugs and biologics that the FDA determines represent a significant improvement over existing therapy, are reviewed in six to eight months after filing. The review process may be extended by the FDA for three additional months to consider certain late-submitted information or clarification regarding information already provided in the submission. The FDA may also refer applications for novel drugs or biological products or products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA or BLA, 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. In addition, before approving an NDA or BLA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP and integrity of the clinical data submitted.

The testing and approval process requires substantial time, effort and financial resources, and each may take many years to complete. Data obtained from clinical activities are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. We may encounter difficulties or unanticipated costs in our efforts to develop our product candidates and secure necessary governmental approvals, which could delay or preclude us from marketing our products.

After the FDA s evaluation of the NDA or BLA and inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the drug or biological product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the

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submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA s satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

Even if the FDA approves a product, the agency may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies be conducted to further assess a drug s safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions through a Risk Evaluation and Mitigation Strategy or other risk management mechanisms, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, some types of changes to the approved product, such as changes in indications, manufacturing changes and labeling, are subject to further testing requirements and FDA review and approval.

*Fast track designation*

The FDA is required to facilitate the development and expedite the review of drugs and biologics that are intended for the treatment of a serious or life-threatening disease or condition for which there is no effective treatment and which demonstrate the potential to address unmet medical needs for the condition. Under the fast track program, the sponsor of a new drug or biologic candidate may request the FDA to designate the product for a specific indication as a fast track product concurrent with or after the filing of the IND for the product candidate. The FDA must determine if the product candidate qualifies for fast track designation within 60 days after receipt of the sponsor s request.

In addition to other benefits, such as the ability to use surrogate endpoints and have more frequent interactions with the FDA, the FDA may initiate review of sections of a fast track product s NDA or BLA before the application is complete. This rolling review is available if the applicant provides and the FDA approves a schedule for the submission of the remaining information and the applicant pays applicable user fees. However, the FDA s time period goal for reviewing a fast track application does not begin until the last section of the NDA or BLA is submitted. In addition, the fast track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

*Priority review*

Under FDA priority review guidelines, a product candidate may be eligible for review within a six to eight month time frame from the time a complete application is accepted for filing. Products regulated by the FDA s Center for Drug Evaluation and Research, or CDER, are eligible for priority review if they provide a significant improvement compared to marketed products in the treatment, diagnosis or prevention of a disease. Products regulated by the FDA s Center for Biologics Evaluation and Research are eligible for priority review if they provide a significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention of a serious or life-threatening disease. A fast track designated product candidate would ordinarily meet the FDA s criteria for priority review.

*Accelerated approval*

Under the FDA s accelerated approval regulations, the FDA may approve a drug or biologic for a serious or life-threatening illness that provides meaningful therapeutic benefit to patients over existing treatments based on a surrogate endpoint that is reasonably likely to predict clinical benefit. In clinical trials, a surrogate endpoint is a

measurement of laboratory or clinical signs of a disease or condition that substitutes for a direct measurement of how a patient feels, functions or survives. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. A product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, would allow the FDA to withdraw the drug from the market on an expedited basis. All promotional materials for drug candidates approved under accelerated regulations are subject to prior review by the FDA.

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*Breakthrough therapy designation*

The FDA is also required to expedite the development and review of the application for approval of drugs that are intended to treat a serious or life-threatening disease or condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Under the breakthrough therapy program, the sponsor of a new drug candidate may request that the FDA designate the drug candidate for a specific indication as a breakthrough therapy concurrent with, or after, the filing of the IND for the drug candidate. The FDA must determine if the drug candidate qualifies for breakthrough therapy designation within 60 days of receipt of the sponsor s request.

*Orphan drugs*

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs or biologics intended to treat a rare disease or condition, which is generally defined as a disease or condition that affects fewer than 200,000 individuals in the United States. Orphan drug designation must be requested before submitting an NDA or BLA. After the FDA grants orphan drug designation, the generic identity of the drug or biologic and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. The first NDA or BLA applicant to receive FDA approval for a particular active ingredient to treat a particular disease with FDA orphan drug designation is entitled to a seven-year exclusive marketing period in the United States for that product, for that indication. During the seven-year exclusivity period, the FDA may not approve any other applications to market the same drug or biologic for the same orphan indication, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity in that it is shown to be safer, more effective or makes a major contribution to patient care. Orphan drug exclusivity does not prevent the FDA from approving a different drug or biologic for the same disease or condition, or the same drug or biologic 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 NDA or BLA application user fee.

*Pediatric information*

Under the Pediatric Research Equity Act of 2003, an NDA, BLA or supplement to an NDA or BLA must contain data from pediatric studies that are adequate to assess the safety and effectiveness of the drug or biological product 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, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Under the Food and Drug Administration Safety and Innovation Act, or FDASIA, the FDA has additional authority to take action against manufacturers not adhering to pediatric study requirements. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan drug designation.

***The Hatch-Waxman Act***

*Abbreviated new drug applications*

In seeking approval for a drug through an NDA, applicants are required to list with the FDA each patent that claims to cover the applicant s product. Upon approval of a drug, each of the patents listed in the application for the drug is then published in the Orange Book. Drugs listed in the Orange Book can, in turn, be cited by potential competitors in support of approval of an ANDA. Generally, an ANDA provides for marketing of a drug product that has the same active ingredients in the same strengths and dosage form as the listed drug and has been shown through

bioequivalence testing to be therapeutically equivalent to the listed drug. Other than the requirement for bioequivalence testing, ANDA applicants are not required to conduct or submit results of preclinical or clinical tests to prove the safety or effectiveness of their drug product. Drugs approved in this way are commonly referred to as generic equivalents to the listed drug, and can often be substituted by pharmacists under prescriptions written for the original listed drug.

The ANDA applicant is required to certify to the FDA concerning any patents listed for the approved product in the FDA s Orange Book. Specifically, the applicant must certify that:

the required patent information has not been filed;

the listed patent has expired;

the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or

the listed patent is invalid or will not be infringed by the new product.

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A certification that the new product will not infringe the already approved product s listed patents or that such patents are invalid is called a Paragraph IV certification. If the ANDA applicant does not challenge the listed patents, the ANDA will not be approved until all the listed patents claiming the referenced product have expired.

If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of a 30 month period, expiration of the patent, settlement of the lawsuit or a decision in the infringement case that the patent involved is deemed invalid or not infringed.

The ANDA also will not be approved until any applicable non-patent exclusivity, such as exclusivity for obtaining approval of a new chemical entity, listed in the Orange Book for the referenced product has expired. Federal law provides a period of five years following approval of a drug containing no previously approved active ingredients during which ANDAs for generic versions of those drugs cannot be received by the FDA, except that the application may be submitted in four years if it contains a Paragraph IV certification. If there is no listed patent in the Orange Book, there may not be a Paragraph IV certification, and thus, no ANDA may be filed before the expiration of the exclusivity period. Federal law provides for a period of three years of exclusivity following approval of a listed drug that contains previously approved active ingredients but is approved in a new dosage form, route of administration or combination, or for a new use, the approval of which was required to be supported by new clinical trials conducted by or for the sponsor, during which the FDA cannot grant effective approval of an ANDA based on that listed drug. Under the BPCA, federal law also provides that periods of patent and non-patent marketing exclusivity listed in the Orange Book for a drug may be extended by six months if the NDA sponsor agrees to conduct and report on pediatric studies identified by the FDA in a written request within the statutory timeframes. Applications under the BPCA are treated as priority applications, with all the benefits that designation confers.

*Patent term extension*

After NDA approval, owners of relevant drug patents may apply for up to a five year patent term extension. The allowable patent term extension is calculated as half of the drug s testing phase, based on the time between IND application and NDA submission, and all of the review phase, based on the time between NDA submission and approval up to a maximum of five years. The time can be shortened if the FDA determines that the applicant did not pursue approval with due diligence. The total patent term after the extension may not exceed 14 years.

For patents that might expire during the application phase, the patent owner may request an interim patent term extension. An interim patent term extension increases the patent term by one year and may be renewed up to four times. For each interim patent term extension granted, the post-approval patent term extension is reduced by one year. The director of the U.S. Patent and Trademark Office must determine that approval of the drug covered by the patent for which a patent term extension is being sought is likely. Interim patent term extensions are not available for a drug for which an NDA has not been submitted.

*Section 505(b)(2) new drug applications*

Most drug products obtain FDA marketing approval pursuant to an NDA or an ANDA. A third alternative is a special type of NDA, commonly referred to as a Section 505(b)(2) NDA, which enables the applicant to rely, in part, on the FDA s previous approval of a similar product, or published literature, in support of its application. Our NDA for ONIVYDE was submitted and reviewed under Section 505(b)(2).

Section 505(b)(2) NDAs often provide an alternate path to FDA approval for new or improved formulations or new uses of previously approved products. Section 505(b)(2) permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference. If the Section 505(b)(2) applicant can establish that reliance on the FDA s previous approval is scientifically appropriate, it may eliminate the need to conduct certain preclinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements to support the change from the approved product. The FDA may then approve the new product for all or some of the label indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant.

To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would. As a result, approval of a Section 505(b)(2) NDA can be stalled until all the listed patents

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claiming the referenced product have expired, until any non-patent exclusivity, such as exclusivity for obtaining approval of a new chemical entity, listed in the Orange Book for the referenced product has expired, and, in the case of a Paragraph IV certification and subsequent patent infringement suit, until the earlier of a 30 month period, settlement of the lawsuit or a decision in the infringement case that the patent involved is deemed invalid or not infringed.

***Combination products***

A combination product is a product comprised of (i) two or more regulated components (i.e., drug/device, biologic/device, drug/biologic or drug/device/biologic) that are physically, chemically, or otherwise combined or mixed and produced as a single entity; (ii) two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products; (iii) a drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where, upon approval of the proposed product, the labeling of the approved product would need to be changed (e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose); or (iv) any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

The FDA is divided into various branches, or Centers, by product type. Different Centers typically review drug, biologic or device applications. In order to review an application for a combination product, the FDA must decide which Center should be responsible for the review. FDA regulations require that the FDA determine the combination product s primary mode of action, or PMOA, which is the single mode of a combination product that provides the most important therapeutic action of the combination product. The Center that regulates that portion of the product that generates the PMOA or that has expertise in the relevant therapeutic area becomes the lead evaluator. If there are two independent modes of action, neither of which is subordinate to the other, the FDA makes a determination as to which Center to assign the product based on consistency with other combination products raising similar types of safety and effectiveness questions or to the Center with the most expertise in evaluating the most significant safety and effectiveness questions raised by the combination product. When evaluating an application, a lead Center may consult other Centers but still retain complete reviewing authority, or it may collaborate with another Center, by which the lead Center assigns review of a specific section of the application to another Center, delegating its review authority for that section. Typically, the FDA requires a single marketing application submitted to the Center selected to be the lead evaluator, although the agency has the discretion to require separate applications to more than one Center. One reason to submit multiple evaluations is if the applicant wishes to receive some benefit that accrues only from approval under a particular type of application, like new drug product exclusivity. If multiple applications are submitted, each application may be evaluated by a different lead Center.

***Biosimilars law***

The Biologics Price Competition and Innovation Act of 2009, or BPCIA, amended the PHSA to create a new licensure framework for biosimilar products, which could ultimately subject our biological products to competition. Under the BPCIA, a manufacturer may submit an application for licensure of a biologic product that is biosimilar to or interchangeable with a referenced, branded biologic product. Previously, there had been no licensure pathway for such biosimilar or interchangeable products. For purposes of the BPCIA, a reference product is defined as the single biological product licensed under a full BLA against which a biological product is evaluated in an application submitted under a follow-on BLA. Biosimilarity sufficient to reference a prior FDA-approved product requires that

there be no differences in conditions of use, route of administration, dosage form, and strength, and no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency. Biosimilarity must be shown through analytical studies, animal studies, and at least one clinical trial, absent a waiver by the Secretary of the U.S. Department of Health & Human Services. A biosimilar product may be deemed interchangeable with a prior approved product if it meets the higher hurdle of demonstrating that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic.

The BPCIA also created a 12-year period of reference product exclusivity, which can be extended to 12 ½ years with pediatric exclusivity. The 12-year exclusivity period begins on the date of first licensure of the reference product under the PHSA and during which the licensure of a follow-on application for a biosimilar or interchangeable product cannot be made effective. During the first four years (or four and one-half years with pediatric exclusivity) of the 12-year period, an application for a biosimilar or interchangeable version of the reference product cannot be submitted to the FDA.

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The BPCIA includes limits on obtaining 12-year reference product exclusivity for certain changes or modifications to the reference product. A separate 12-year reference product exclusivity period does not apply to:

- a BLA supplement for the product that is the reference product;
- a subsequent BLA filed by the same reference product sponsor or manufacturer (or a licensor, predecessor in interest, or other related entity) for a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device or strength; or
- a modification to the structure of the biological product that does not result in a change in safety, purity or potency.

The FDA has not yet issued proposed regulations setting forth its interpretation of the BPCIA s provisions but has issued guidance documents in 2015 related to BPCIA implementation concerning biosimilarity and interchangeability, BLA submission requirements and exclusivity.

In addition to creating a 12-year period of reference product exclusivity, the BPCIA clarifies the interaction of that exclusivity with orphan drug exclusivity, such that the licensure of a biosimilar or interchangeable version of a reference product that was designated and approved as an orphan drug may only occur after the later of the expiration of any applicable seven-year orphan drug exclusivity or the 12-year reference product exclusivity (or seven and one-half years and 12 ½ years with pediatric exclusivity).

Like pediatric exclusivity applicable to drug products approved under the FDCA, pediatric exclusivity applicable to biological reference products is subject to an exception. Pediatric exclusivity will not apply to either the 12-year reference product or the seven-year orphan drug exclusivity periods if the FDA determines later than nine months prior to the expiration of such period that the study reports a BLA sponsor submitted in response to a written request for pediatric studies met the terms of that request.

Our investigational biological products, if approved, could be considered reference products entitled to 12-year exclusivity. Even if our products are considered to be reference products eligible for exclusivity, another company could market a competing version of any of our biological products if the FDA approves a full BLA for such product containing the sponsor s own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of their product.

The BPCIA also sets forth a complex mechanism for resolving patent disputes that involves a step-wise exchange of information prior to the initiation of a patent infringement lawsuit against a biosimilar or interchangeable product sponsor. Unlike the Hatch-Waxman Act, the BPCIA provides no automatic stay on approval of a biosimilar or interchangeable product application.

***Overview of FDA regulation of companion diagnostics***

We are developing *in vitro* and *in vivo* diagnostics for use in selecting the patients that we believe will respond to our cancer therapeutics.

The FDA published final guidance in July 2014 that addresses issues critical to developing *in vitro* companion diagnostics. The guidance provides that *in vitro* companion diagnostics that are essential for the safe and effective use of a corresponding therapeutic product must be approved contemporaneously with that therapeutic in most circumstances. Based on the guidance and the FDA s past treatment of companion diagnostics, we believe that the FDA will likely require one or more of our *in vitro* diagnostics to obtain PMA in conjunction with approval of the associated therapeutic, which will involve coordination of review by CDER and by the FDA s Center for Devices and Radiological Health Office of In Vitro Diagnostics and Radiological Health. Our *in vivo* diagnostics, which are in the form of imaging agents, are regulated as drugs by CDER for therapeutic uses. As such, they are generally subject to the regulatory requirements applicable to other new drug candidates.

Diagnostic tests determined by the FDA to be useful, but not essential, for the safe and effective use of a corresponding therapeutic product are also subject to the same medical device pathways, but their clearance or approval would not be subject to a coordinated review of the diagnostic test and the therapeutic product.

The FDA classifies medical devices into one of three classes. Devices deemed to pose lower risk are placed in either Class I or II, which requires the manufacturer to submit to the FDA a premarket notification requesting permission for commercial distribution. Some low risk devices are exempt from this requirement. Devices deemed by the FDA to pose the greatest risk, such as life-sustaining, life-supporting or implantable devices, or devices deemed not substantially equivalent to a previously cleared 510(k) device, are placed in Class III, requiring a PMA. A medical device, including an *in vitro* diagnostic, or IVD, to be commercially distributed in the United States must receive either 510(k) clearance or PMA (or be a Class I exempt device that does not require pre-market review) from the FDA prior to marketing.

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*510(k) clearance pathway*

If any of the diagnostic products under development were determined by FDA not to be essential to the safe and effective prescription of a corresponding therapeutic product, it is possible that the diagnostic test could require 510(k) clearance. The FDA s 510(k) clearance pathway usually takes from three to twelve months, but it can take significantly longer. The FDA may require additional information, including clinical data, to make a determination regarding substantial equivalence.

After a device receives 510(k) clearance, any modification that could significantly affect its safety or effectiveness, or that would constitute a new or major change in its intended use, would require a new 510(k) clearance or, depending on the modification, a PMA. The FDA requires each manufacturer to determine whether the proposed change requires submission of a 510(k) notice or a PMA, but the FDA can review any such decision and can disagree with a manufacturer s determination. If the FDA disagrees with a manufacturer s determination, the FDA can require the manufacturer to cease marketing and/or recall the modified device until 510(k) clearance or a PMA is obtained. If the FDA requires us to seek 510(k) clearance or a PMA for any modifications to a previously cleared product, we may be required to cease marketing or recall the modified device until we obtain this clearance or approval. Also, in these circumstances, we may be subject to significant regulatory fines or penalties.

*PMA pathway*

Devices deemed by the FDA to pose the greatest risk, such as life-sustaining, life supporting or implantable devices, or devices deemed not substantially equivalent to a previously 510(k) cleared device or a preamendment Class III device for which PMA applications have not been called, are placed in Class III requiring PMA. The PMA pathway requires proof of the safety and effectiveness of the device to the FDA s satisfaction. The PMA pathway generally takes from one to three years or even longer from submission of the application. Most companion diagnostic tests have been classified as Class III devices subject to the PMA pathway.

A PMA application for an IVD must provide extensive preclinical and clinical trial data. Preclinical data for an IVD includes many different tests, including how reproducible the results are when the same sample is tested multiple times by multiple users at multiple laboratories. The clinical data need to establish that the test is sufficiently safe, effective and reliable in the intended use population. In addition, the FDA must be convinced that a device has clinical utility, meaning that an IVD provides information that is clinically meaningful. A biomarker s clinical significance may be obvious, or the applicant may be able to rely upon published literature or submit data to show clinical utility.

A PMA application also must provide information about the device and its components regarding, among other things, device design, manufacturing and labeling. The sponsor must pay an application fee.

As part of the PMA review, the FDA will typically inspect the manufacturer s facilities for compliance with Quality System Regulation, or QSR, requirements, which impose elaborate design control, testing, manufacturing, control, documentation and other quality assurance procedures.

Upon submission, the FDA determines if the PMA application is sufficiently complete to permit a substantive review, and, if so, the FDA accepts the application for filing. The FDA then commences an in-depth review of the PMA application. The entire process typically takes one to three years, but may take longer. The review time is often significantly extended as a result of the FDA asking for more information or clarification of information already provided. The FDA also may respond with a not approvable determination based on deficiencies in the application and require additional clinical trials that are often expensive and time-consuming and can substantially delay approval. During the review period, an FDA advisory committee, typically a panel of clinicians, likely will be convened to

review the application and recommend to the FDA whether, or upon what conditions, the device should be approved. Although the FDA is not bound by the advisory panel decision, the panel s recommendation is important to the FDA s overall decision making process.

If the FDA s evaluation of the PMA application is favorable, the FDA typically issues an approvable letter requiring the applicant s agreement to specific conditions, such as changes in labeling, or specific additional information, such as submission of final labeling, in order to secure final approval of the PMA. If the FDA concludes that the applicable criteria have been met, the FDA will issue a PMA for the approved indications, which can be more limited than those originally sought by the manufacturer. The PMA can include post-approval conditions that the FDA believes necessary to ensure the safety and effectiveness of the device, including, among other things, restrictions on labeling, promotion, sale and distribution. Failure to comply with the conditions of approval can result in material adverse enforcement action, including the loss or withdrawal of the approval.

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Even after approval of a PMA, a new PMA or PMA supplement may be required in the event of a modification to the device, its labeling or its manufacturing process. Supplements to a PMA often require the submission of the same type of information required for an original PMA, except that the supplement is generally limited to the information needed to support the proposed change from the product covered by the original PMA.

*Clinical trials*

A clinical trial is almost always required to support a PMA application. All clinical trials of investigational devices must be conducted in compliance with the FDA s requirements. If an investigational device could pose a significant risk to patients pursuant to FDA regulations, the FDA must approve an Investigational Device Exemption, or IDE, application prior to initiation of investigational use. IVD trials usually do not require an IDE, as the FDA does not judge them to be a significant risk because the results do not affect the patients in the study. However, for a trial where the IVD result directs the therapeutic care of patients with cancer (companion diagnostics), we believe that the FDA would consider the investigation to present significant risk and require an IDE.

An IDE application must be supported by appropriate data, such as laboratory test results, showing that it is safe to test the device in humans and that the testing protocol is scientifically sound. The FDA typically grants IDE approval for a specified number of patients. A nonsignificant risk device does not require FDA approval of an IDE. Both significant risk and nonsignificant risk investigational devices require approval from IRBs at the study centers where the device will be used.

During the trial, the sponsor must comply with the FDA s IDE requirements for investigator selection, trial monitoring, reporting and record keeping. The investigators must obtain patient informed consent, rigorously follow the investigational plan and study protocol, control the disposition of investigational devices and comply with all reporting and record keeping requirements. Prior to granting PMA, the FDA typically inspects the records relating to the conduct of the study and the clinical data supporting the PMA application for compliance with applicable requirements.

Although the QSR does not fully apply to investigational devices, the requirement for controls on design and development does apply. The sponsor also must manufacture the investigational device in conformity with the quality controls described in the IDE application and any conditions of IDE approval that the FDA may impose with respect to manufacturing.

*Post-market*

After a device is on the market, numerous regulatory requirements apply. These requirements include: the QSR, labeling regulations, the FDA s general prohibition against promoting products for unapproved or off label uses, the Medical Device Reporting regulation, which requires that manufacturers report to the FDA if their device may have caused or contributed to a death or serious injury or malfunctioned in a way that would likely cause or contribute to a death or serious injury if it were to recur, and the Reports of Corrections and Removals regulation, which requires manufacturers to report recalls and field actions to the FDA if initiated to reduce a risk to health posed by the device or to remedy a violation of the FDCA.

The FDA enforces these requirements by inspection and market surveillance. If the FDA finds a violation, it can institute a wide variety of enforcement actions, ranging from a public warning letter to more severe sanctions such as: fines, injunctions and civil penalties; recall or seizure of products; operating restrictions, partial suspension or total shutdown of production; refusing requests for PMA of new products; withdrawing PMAs already granted; and criminal prosecution.

***Other regulatory requirements***

Any drug or biological products manufactured or distributed by us pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse drug experiences. 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.

The FDA may impose a number of post-approval requirements as a condition of approval of an NDA or BLA. For example, the FDA may require post-marketing testing, including Phase 4 clinical trials, and surveillance to further assess and monitor the product s safety and effectiveness after commercialization. Regulatory approval of oncology products often requires that patients in clinical trials be followed for long periods to determine the overall survival benefit of the drug or biologic.

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In addition, drug and biologic manufacturers and other entities involved in the manufacture and distribution of approved drugs and biological products are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. The FDA was also granted new inspection authorities under FDASIA. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation 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 areas of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards 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 trials to assess new safety risks or imposition of distribution or other restrictions under a Risk Evaluation and Mitigation Strategy program. Other potential consequences include, among other things:

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

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs and biologics may be promoted only for the approved indications and in accordance with the provisions of the approved label. 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.

***Additional provisions***

*Anti-kickback and false claims laws*

In addition to FDA restrictions on marketing of pharmaceutical products, pharmaceutical companies that participate in federal healthcare programs like Medicare or Medicaid are subject to various U.S. federal and state laws that may restrict certain marketing practices. These laws include but are not limited to anti-kickback statutes and false claims

statutes. The federal anti-kickback statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item or service reimbursable under Medicare, Medicaid or other federally financed healthcare programs. The Patient Protection and Affordable Care Act as amended by the Health Care Education and Reconciliation Act of 2010, collectively the Health Care Reform Laws, amended the intent element of the anti-kickback statute such that liability under the statute can be proved even if a person or entity does not have actual knowledge of the statute or specific intent to violate it. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers on the other. Violations of the anti-kickback statute are punishable by imprisonment, criminal fines, civil monetary penalties and exclusion from participation in federal healthcare programs. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution or other regulatory sanctions, the exemptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor. In addition to the federal anti-kickback statute, the federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, or HIPAA, makes it a crime to knowingly and willfully execute or attempt to execute a scheme to defraud any healthcare benefit program

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The federal civil False Claims Act prohibits any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government, or knowingly making, or causing to be made, a false statement to have a false claim paid. Government enforcement agencies and private whistleblowers have initiated investigations or brought private lawsuits against pharmaceutical companies for a variety of allegedly improper promotional or marketing activities, such as allegedly inflating drug prices they report to pricing services, which in turn were used by the government to set Medicare and Medicaid reimbursement rates, for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product, or for engaging in promotion for off-label uses. Additionally, the Health Care Reform Laws amended the federal False Claims Act such that a violation of the federal anti-kickback statute can serve as a basis for liability under the False Claims Act. In addition to the federal civil False Claims Act, the federal false statements statute prohibits, among other things, knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services.

The majority of states also have statutes or regulations similar to the federal anti-kickback statute and/or False Claims Act, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor. In addition, the federal transparency law under the Health Care Reform Laws, known as the Open Payments program, requires manufacturers of drugs, devices, biologics and medical supplies reimbursable under Medicare or Medicaid to report to the Department of Health and Human Services information related to payments and other transfers of value to physicians and teaching hospitals, as well as physician ownership and investment interests, and provides for public reporting of the data reported by manufacturers.

*Government price reporting*

We are required to report certain price data and pay certain rebates to the U.S. government as a condition of participation in federal healthcare programs. Medicaid is jointly administered by federal and state governments for the benefit of low income and certain disabled beneficiaries. Under the Medicaid Drug Rebate Program, we are required to pay a rebate for each unit of product reimbursed by the state Medicaid programs. For most brand name drugs, including ONIVYDE, the total Medicaid rebate amount consists of the basic rebate and the additional rebate. The basic rebate is set by law as the greater of 23.1% of the drug s average manufacturer price, or AMP, or the difference between AMP and the best price for the drug available from us to any commercial customer (with limited exceptions). The additional rebate is designed to capture price increases that outpace inflation (measured by the Consumer Price Index Urban). The rebate amount is calculated each quarter based on our report of current AMP and best price figures for each of our products to the Centers for Medicare & Medicaid Services, or CMS, the federal agency that administers the Medicaid and Medicare programs. The requirements for calculating AMP and best price are complex. We are required to report any revisions to AMP or best price previously reported within a certain period, which revisions could affect our Medicaid rebate liability for prior quarters. In addition, if we fail to provide information timely or we are found to have knowingly submitted false information to the government, the Medicaid statute provides for civil monetary penalties.

Medicare is a federal program that is administered by the federal government that covers individuals age 65 and over as well as those with certain disabilities or other conditions irrespective of age. Medicare Part B generally covers drugs that must be administered by physicians or other healthcare practitioners, are provided in connection with certain durable medical equipment, or are certain oral anti-cancer drugs and certain oral immunosuppressive drugs. Medicare Part B pays for such drugs furnished by physicians under a payment methodology based on the average sales price, or ASP, of the drugs. We report ASP for ONIVYDE. Manufacturers, including us, are required to provide ASP information to CMS on a quarterly basis. The manufacturer-submitted information is used to calculate Medicare payment rates. The payment rates for drugs in the hospital outpatient setting are also paid on a methodology based on ASP, although that could change on a calendar year basis. CMS also has the statutory authority to adjust payment

rates for specific drugs outside the hospital outpatient setting based on a comparison of ASP payment rates to widely available market prices or to AMP, which could decrease Medicare payment rates. If a manufacturer is found to have made a misrepresentation in the reporting of ASP, the governing statute provides for civil monetary penalties.

Federal law requires that any company that participates in the Medicaid Drug Rebate Program also participate in the Public Health Service s, or PHS , 340B drug pricing discount program in order for federal funds to be available for the manufacturer s drugs under Medicaid and Medicare Part B. The 340B pricing program requires participating manufacturers to agree to charge statutorily-defined covered entities no more than the 340B ceiling price for the manufacturer s covered outpatient drugs. These 340B covered entities include a variety of community health clinics and other entities that receive health services grants from the PHS, as well as hospitals that serve a disproportionate share of low-income patients. The 340B ceiling price is calculated using a statutory formula, which is based on the AMP and Medicaid rebate amount for the covered outpatient drug, as calculated under the Medicaid Drug Rebate Program.

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In order to be eligible to have our products paid for with federal funds under the Medicaid and Medicare Part B programs and purchased by certain federal agencies and grantees, we participate in the Department of Veterans Affairs, or VA, Federal Supply Schedule, or FSS, pricing program. As part of this program, we are obligated to make our products available for procurement on an FSS contract under which we must comply with standard government terms and conditions and charge a price that is no higher than the statutory Federal Ceiling Price, or FCP, to the VA, Department of Defense, Coast Guard and the PHS. The FCP is based on the non-federal average manufacturer price, or Non-FAMP, which we calculate and report to the VA on a quarterly and annual basis. Pursuant to applicable law, knowing provision of false information in connection with a Non-FAMP filing can subject a manufacturer to penalties of $100,000 for each item of false information. These obligations also contain extensive disclosure and certification requirements.

Under Section 703 of the National Defense Authorization Act for FY 2008, we are required to pay quarterly rebates on utilization of innovator products that are dispensed through the Tricare retail pharmacy network to Tricare beneficiaries. The rebates are calculated as the difference between the annual Non-FAMP and FCP. We are required to list our covered products on a Tricare Agreement in order for these products to be eligible for Department of Defense formulary inclusion.

If we overcharge the government in connection with our FSS contract or the Tricare retail pharmacy program, whether due to a misstated FCP or otherwise, we are required to refund the difference to the government. Failure to make necessary disclosures and/or to identify contract overcharges can result in allegations against us under the False Claims Act and other laws and regulations. Unexpected refunds to the government, and responding to a government investigation or enforcement action, would be expensive and time-consuming, and could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

***Data Protection***

We are subject to data protection laws and regulations (i.e., laws and regulations that address privacy and data security). The legislative and regulatory landscape for data protection continues to evolve, and in recent years there has been an increasing focus on privacy and data security issues. In the United States, numerous federal and state laws and regulations, including state data breach notification laws, state health information privacy laws and federal and state consumer protection laws govern the collection, use, disclosure and protection of health-related and other personal information. Failure to comply with data protection laws and regulations could result in government enforcement actions (which could include civil or criminal penalties), private litigation and/or adverse publicity and could negatively affect our operating results and business. In addition, we may obtain health information from third parties (e.g., healthcare providers who prescribe our products) that are subject to privacy and security requirements under HIPAA. We could be subject to criminal penalties if we knowingly obtain or disclose individually identifiable health information in a manner that is not authorized or permitted.

***Foreign regulation***

In order to market any therapeutic or diagnostic product outside of the United States, we need to comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of our products. Whether or not we obtain FDA approval for a product, we need to 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 administrative review periods. The time required to obtain approval in other countries might differ from and be longer than that required to obtain FDA approval. 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.

The EMA grants orphan medicinal product designation to promote the development of products that may offer therapeutic benefits for life-threatening or chronically debilitating conditions affecting not more than five in 10,000 people in the European Union. In addition, orphan medicinal product designation can be granted if the drug is intended for a life threatening, seriously debilitating or serious and chronic condition and without incentives it is unlikely that sales of the drug in the European Union would be sufficient to justify developing the drug. Orphan medicinal product designation is only available if there is no other satisfactory method approved in the European Union of diagnosing, preventing or treating the condition, or if such a method exists, the proposed orphan medicinal product will be of significant benefit to patients. Orphan medicinal product designation provides opportunities for free protocol assistance and fee reductions for access to the centralized regulatory procedures. Orphan medicinal product designation also provides ten years of market exclusivity following drug approval. The exclusivity period may be reduced to six years if the designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity.

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*Foreign Corrupt Practices Act*

Various federal and foreign laws govern our international business practices with respect to payments to government officials. Those laws include the U.S. Foreign Corrupt Practices Act, or FCPA, which prohibits U.S. companies and their representatives from paying, offering to pay, promising or authorizing the payment of anything of value to any foreign government official, government staff member, political party or political candidate for the purpose of obtaining or retaining business or to otherwise obtain favorable treatment or influence a person working in an official capacity. In many countries, the healthcare professionals we may interact with may meet the FCPA s definition of a foreign government official. The FCPA also requires public companies to make and keep books and records that accurately and fairly reflect their transactions and to devise and maintain an adequate system of internal accounting controls.

We are subject also to the U.K. Bribery Act 2010, or Bribery Act, which proscribes giving and receiving bribes in the public and private sectors, bribing a foreign public official, and failing to have adequate procedures to prevent employees and other agents from giving bribes. U.S. companies that conduct business in the United Kingdom generally will be subject to the Bribery Act. Penalties under the Bribery Act include potentially unlimited fines for companies and criminal sanctions for corporate officers under certain circumstances. Other countries have enacted similar anti-corruption laws and/or regulations.

***New legislation and regulations***

From time to time, legislation is drafted, introduced and passed in Congress that could significantly change the statutory provisions governing the testing, approval, manufacturing and marketing of products regulated by the FDA.

In addition to new legislation, FDA regulations and policies are often revised or interpreted by the agency in ways that may significantly affect our business and our products. It is impossible to predict whether further legislative changes will be enacted or whether FDA regulations, guidance, policies or interpretations changed or what the effect of such changes, if any, may be.

For example, the FDASIA, which was enacted in 2012, is a broad, sweeping law that establishes new user fee programs and provides the FDA with new authority in the areas of drugs, biologics and medical devices. In particular, the FDASIA provides the FDA with new inspection authorities. A drug or biologic will be considered adulterated, with possible resulting civil and criminal penalties, if the owner or operator of the establishment where it is made, processed, packed or held delays, denies, limits or refuses inspection. The FDASIA also replaces the biennial inspection schedule for drugs and biologics with a risk-based inspection schedule. The law grants the FDA authority to require a drug or biologics manufacturer to provide, in advance or instead of an inspection, and at the manufacturer s expense, any records or other information that the agency may otherwise inspect at the facility. The FDASIA also permits the FDA to share inspection information with foreign governments under certain circumstances. The FDASIA also provides the FDA with additional authority to exercise against manufacturers of drugs or biologics that are not adhering to pediatric study requirements, which apply even if the manufacturer is not seeking to market the drug or biologic to pediatric patients.

In addition, the Health Care Reform Laws were enacted in the United States in March 2010 and contain provisions that may reduce the profitability of drug products, including, for example, increased rebates for drugs sold to Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies share of sales to federal healthcare programs.

***Pharmaceutical coverage, pricing and reimbursement***

The containment of healthcare costs has become a priority of federal, state and foreign governments, and the prices of drugs have been a focus in this effort. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid healthcare costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. Adoption of such controls and measures, and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for ONIVYDE or any other drug products for which we obtain regulatory approval and could adversely affect our net revenue and results.

Significant uncertainty exists as to the coverage and reimbursement status of ONIVYDE or any other drug products for which we obtain regulatory approval. Sales of ONIVYDE or any of our product candidates, if approved, depend in significant part on the availability of adequate financial coverage and reimbursement from third-party payors, including government health programs such as Medicare and Medicaid, commercial health insurers and managed care organizations.

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Political, economic and regulatory influences are subjecting the healthcare industry in the United States to fundamental changes. There have been, and we expect there will continue to be, legislative and regulatory proposals to change the healthcare system in ways that could impact our ability to sell our products profitably. The Health Care Reform Laws expanded healthcare coverage within the United States, primarily through the imposition of health insurance mandates on employers and individuals and expansion of the Medicaid program. This law substantially changes the way healthcare is financed by both governmental and private insurers, and significantly impacts the pharmaceutical industry. The Healthcare Reform Laws contain a number of provisions that may impact our business and operations. On February 1, 2016, CMS issued final regulations to implement the changes to the Medicaid Drug Rebate program under the Healthcare Reform Laws. These regulations become effective, in general, on April 1, 2016. We are evaluating the impact of these regulations on our business and operations.

The Healthcare Reform Laws also obligate the Health Resources and Services Administration, or HRSA, the agency which administers the 340B program, to create regulations and processes to improve the integrity of the 340B program and to update the agreement that manufacturers must sign to participate in the 340B program to obligate a manufacturer to offer the 340B price to covered entities if the manufacturer makes the drug available to any other purchaser at any price and to report the ceiling prices for its drugs to the government. HRSA recently issued a proposed regulation regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities, as well as proposed omnibus guidance that addresses many aspects of the 340B program, including a proposed expansion of manufacturer recordkeeping requirements and 340B ceiling price restatement and refund obligations. HRSA is currently expected to issue additional proposed regulations in 2016. Any final regulation could affect our obligations under the 340B program in ways we cannot anticipate. Further, legislation may be introduced that, if passed, would further expand the 340B program to additional covered entities or would require participating manufacturers to agree to provide 340B discounted pricing on drugs used in the inpatient setting.

In addition, beginning April 1, 2013, Medicare payments for all items and services, including drugs and biologics, were reduced by 2% under the sequestration required by the Budget Control Act of 2011, as amended by the American Taxpayer Relief Act of 2012. Subsequent legislation extended the 2% reduction, on average, to 2025. These cuts reduce reimbursement payments related to our products, which could potentially negatively impact our revenue.

Medicare Part D provides coverage to enrolled Medicare patients for certain drugs, such as self-administered drugs (i.e., drugs that do not need to be injected or otherwise administered by a physician). Medicare Part D is administered by private prescription drug plans approved by the U.S. government, and each drug plan establishes its own Medicare Part D formulary for prescription drug coverage and pricing, which the drug plan may modify from time to time. The prescription drug plans negotiate pricing with manufacturers and may condition formulary placement on the availability of manufacturer discounts. Manufacturers, including us, are required to provide a 50% discount on brand name prescription drugs utilized by Medicare Part D beneficiaries when those beneficiaries reach the coverage gap in their drug benefits.

Third-party payors decide which drugs they will pay for and establish reimbursement and co-pay levels. The growing emphasis on managed care in the United States has increased and we expect will continue to increase the pressure on drug pricing. Third-party payors are increasingly challenging the prices charged for medical products and services and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. If these third-party payors do not consider our products to be cost-effective compared to other available therapies, they may not cover our products as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products at a profit. In order to secure coverage and reimbursement for any product that might be approved for sale, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain

FDA or other comparable regulatory approvals. Even with clinical trials, our product candidates may be considered less safe, less effective or less cost-effective than other products, and third-party payors may not provide coverage and reimbursement for our products or any of our product candidates that we commercialize, in whole or in part.

The process for determining whether a payor will provide coverage for a drug product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the drug product once coverage is approved. Third-party payors may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the approved drugs for a particular indication, and a payor s decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Third-party reimbursement may not be sufficient to enable us to maintain price levels high enough to realize an appropriate return on our investment in product development. In addition, coverage policies, third-party reimbursement rates and drug pricing regulation may change at any time. Thus, even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future. The marketability of any products for which we receive regulatory approval for commercial sale may also suffer if the government and third-party payors fail to provide adequate coverage and reimbursement.

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Payors also are increasingly considering new metrics as the basis for reimbursement rates, such as ASP, AMP and actual acquisition cost. The existing data for reimbursement based on these metrics is relatively limited, although certain states have begun to survey acquisition cost data for the purpose of setting Medicaid reimbursement rates. CMS surveys and publishes retail community pharmacy acquisition cost information in the form of National Average Drug Acquisition Cost, or NADAC, files to provide state Medicaid agencies with a basis of comparison for their own reimbursement and pricing methodologies and rates. It may be difficult to project the impact of these evolving reimbursement mechanics on the willingness of payors to cover our products.

For Medicare and other health insurance programs in the United States, Healthcare Common Procedure Coding System codes, or HCPCS codes, are used to ensure that claims for certain items and services (including most drugs) are submitted and adjudicated in an orderly and consistent manner. The HCPCS code set is maintained by CMS and applications for HCPCS codes are submitted to CMS. Based primarily on the existence of an HCPCS code that appropriately describes a product, a new product may be assigned to a new or existing HCPCS code and may be the only product or one of several products described by that HCPCS code. For many drug HCPCS codes, CMS sets the Medicare payment rate for the code. Presently, HCPCS code J9206 described as Irinotecan Injection exists. If ONIVYDE were to be assigned to this HCPCS code, the payment rate for ONIVYDE would not be based exclusively on its own pricing information but on pricing information for all products assigned to that HCPCS code which, at present, includes both brand name and generic products. This payment rate may be insufficient to enable us to fully realize commercial success.

Beyond the United States, pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies. For example, the European Union provides options for its member states to restrict the range of drug products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. European Union member states may approve a specific price for a drug product or may instead adopt a system of direct or indirect controls on the profitability of the company placing the drug product on the market. Other member states allow companies to fix their own prices for drug products, but monitor and control company profits. The downward pressure on healthcare costs in general, particularly prescription drugs, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert competitive pressure that may reduce pricing within a country. There can be no assurance that any country that has price controls or reimbursement limitations for drug products will allow favorable reimbursement and pricing arrangements for any of our products.

**Employees**

As of January 31, 2016, we had 426 full-time employees, including a total of 103 employees with M.D. or Ph.D. degrees. Of these full-time employees, 277 employees are engaged in research, development and manufacturing. None of our employees is represented by a labor union or covered by collective bargaining agreements. We consider our relationship with our employees to be good.

**Segment, Geographic and Financial Information**

Operating segments are defined as components of an enterprise engaging in business activities for which discrete financial information is available and regularly reviewed by the chief operating decision maker in deciding how to allocate resources and in assessing performance. We view our operations and manage our business in one operating segment and we operate in only one geographic region.

Financial information about (1) our net product revenues and other revenues, net loss per share available to common stockholders and our total assets is provided in our consolidated financial statements included in this Annual Report on Form 10-K and (2) our research and development expenses in each of the last three fiscal years is provided in Item 7. Management s Discussion and Analysis of Financial Condition and Results of Operations.

**Our Corporate Information**

We were originally incorporated in the Commonwealth of Massachusetts in 1993 and reincorporated under the laws of the State of Delaware in October 2010. Our principal executive offices are located at One Kendall Square, Suite B7201, Cambridge, MA 02139, and our telephone number is (617) 441-1000.

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**Information Available on the Internet**

We maintain a website with the address *www.merrimack.com*. We are not including the information contained on our website as a part of, or incorporating it by reference into, this Annual Report on Form 10-K. Our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and all amendments to those reports, are available to you free of charge through the SEC Filings link in the Investors section of our website as soon as reasonably practicable after those materials have been electronically filed with, or furnished to, the Securities and Exchange Commission, or the SEC. We also make available on our website our corporate governance guidelines, the charters for our audit committee, corporate governance and nominating committee, organization and compensation committee and executive committee, and our code of business conduct and ethics, which applies to our directors, officers and employees, and such information is available in print and free of charge to any of our stockholders who requests it. In addition, we intend to disclose on our website any amendments to, or waivers from, our code of business conduct and ethics that are required to be publicly disclosed pursuant to rules of the SEC.

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## Item 1A. Risk Factors

*The following risk factors and other information included in this Annual Report on Form 10-K should be carefully considered. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. Please see page 2 of this Annual Report on Form 10-K for a discussion of some of the forward-looking statements that are qualified by these risk factors. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected.*

### Risks Related to Our Financial Position and Need for Additional Capital

***We have incurred significant losses since our inception. We expect to incur losses for the foreseeable future and may never achieve or maintain profitability.***

Since inception, we have incurred significant operating losses. Our net loss was $147.8 million for the year ended December 31, 2015, $83.6 million for the year ended December 31, 2014 and $130.7 million for the year ended December 31, 2013. As of December 31, 2015, we had an accumulated deficit of $802.2 million. To date, we have financed our operations primarily through private placements of our convertible preferred stock, collaborations, public offerings of our securities and secured debt financings. We have devoted substantially all of our efforts to research and development, including clinical trials, and recently to commercialization of our first product, ONIVYDE (MM-398). We have not completed development of or commercialized any other therapeutic product candidates or diagnostics other than ONIVYDE. We expect to continue to incur significant expenses and increasing operating losses for at least the next several years. We anticipate that our expenses will increase substantially as we:

- initiate or continue clinical trials of our clinical stage product candidates;
- continue the research and development of our other product candidates;
- seek to discover additional product candidates;
- seek regulatory approvals for our product candidates that successfully complete clinical trials, including ONIVYDE in additional indications;
- continue to develop our sales, marketing and distribution infrastructure and scale up manufacturing capabilities to commercialize ONIVYDE and other products for which we may seek regulatory approval; and
- add operational, financial and management information systems and personnel, including personnel to support our product development and commercialization efforts.

To become and remain profitable, we must succeed in developing and commercializing products with significant market potential. This will require us to be successful in a range of challenging activities, including discovering

product candidates, completing preclinical testing and clinical trials of our product candidates, obtaining regulatory approval for these product candidates and manufacturing, marketing and selling those products for which we may seek regulatory approval. We are only in the preliminary stages of some of these activities for most of our product candidates, and our commercial activities for ONIVYDE are nascent. We may never succeed in these activities and may never generate revenues that are significant or large enough to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our company and could impair our ability to raise capital, expand our business, diversify our product offerings or continue our operations. A decline in the value of our company could also cause our stockholders to lose all or part of their investment.

***Our substantial indebtedness may limit cash flow available to invest in the ongoing needs of our business.***

We currently have, and will continue to have, a significant amount of indebtedness. In July 2013, we issued $125.0 million aggregate principal amount of 4.50% convertible senior notes due 2020, or convertible notes, and in December 2015, we issued $175.0 million aggregate principal amount of 11.50% senior secured notes due 2022, or 2022 notes. We could in the future incur additional indebtedness beyond such amounts.

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Our substantial debt combined with our other financial obligations and contractual commitments could have significant adverse consequences, including:

- requiring us to dedicate a substantial portion of cash flow from operations to the payment of interest on, and principal of, our debt, which will reduce the amounts available to fund working capital, capital expenditures, product development efforts and other general corporate purposes;
- increasing our vulnerability to adverse changes in general economic, industry and market conditions;
- obligating us to restrictive covenants that may reduce our ability to take certain corporate actions or obtain further debt or equity financing;
- limiting our flexibility in planning for, or reacting to, changes in our business and the industry in which we compete; and
- placing us at a competitive disadvantage compared to our competitors that have less debt or better debt servicing options.

We intend to satisfy our current and future debt service obligations with our existing cash and cash equivalents and marketable securities and funds from external sources. However, we may not have sufficient funds or may be unable to arrange for additional financing to pay the amounts due under our existing debt. Funds from external sources may not be available on acceptable terms, if at all. In addition, a failure to comply with the covenants under our existing debt instruments could result in an event of default under those instruments. In the event of an acceleration of amounts due under our debt instruments as a result of an event of default, including upon the occurrence of an event that would reasonably be expected to have a material adverse effect on our business, operations, properties, assets or condition or a failure to pay any amount due, we may not have sufficient funds or may be unable to arrange for additional financing to repay our indebtedness or to make any accelerated payments, and the lenders could seek to enforce security interests in the collateral securing such indebtedness. In addition, the covenants under our existing debt instruments and the pledge of our assets as collateral limit our ability to obtain additional debt financing.

***Servicing our debt requires a significant amount of cash, and we may not have sufficient cash flow from our business to pay our obligations.***

Our ability to make scheduled payments of the principal of, to pay interest on or to refinance our indebtedness depends on our future performance, which is subject to economic, financial, competitive and other factors beyond our control. We currently do not generate cash flow from operations and, in the future, our business may not generate cash flow from operations sufficient to service our debt and make necessary capital expenditures. If we are unable to generate cash flow, we may be required to adopt one or more alternatives, such as selling assets, restructuring debt or obtaining additional equity or debt financing on terms that may be unfavorable to us or highly dilutive. Our ability to refinance our indebtedness will depend on the capital markets and our financial condition at such time. We may not be able to engage in any of these activities at all or engage in these activities on desirable terms, which could result in a default on our debt obligations or future indebtedness.

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

We will need substantial additional funding in connection with our continuing operations. We expect our research and development expenses to continue to increase in connection with our ongoing activities, particularly as we continue the research, development and clinical trials of, and seek regulatory approval for, our product candidates. In addition, we expect to incur significant commercialization expenses for product sales, marketing, manufacturing and distribution related to ONIVYDE and any other product for which we obtain regulatory approval in the future. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce or eliminate our research and development programs or commercialization efforts.

At our currently planned spending rates, we believe that our existing financial resources, together with anticipated net product revenues and net royalty payments from sales of ONIVYDE and the net milestone payments and reimbursements we expect to receive under our Baxalta collaboration, will be sufficient to fund our operations for at least the next twelve months. We have based this estimate on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Because of the numerous risks and uncertainties associated with the development and commercialization of our product candidates, and the extent to which we utilize collaborations with third parties to participate in their development and commercialization, we are unable to estimate the amounts of increased capital outlays and operating expenditures associated with our current and anticipated clinical trials. Our future capital requirements will depend on many factors, including:

- the amount of net product revenues realized from ONIVYDE commercial sales

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- the progress and results of the clinical trials of our clinical stage product candidates;
- the success of our collaborations with Baxalta and PharmaEngine related to ONIVYDE and any future collaborations with other parties that we may enter into;
- the timing and amount of anticipated milestone payments and cost sharing reimbursements related to ONIVYDE that we may receive from Baxalta;
- the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials for our other product candidates;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs of commercial activities, including product sales, marketing, manufacturing and distribution;
- the costs of preparing, filing and prosecuting patent applications and maintaining, enforcing and defending intellectual property-related claims;
- the extent to which we acquire or invest in businesses, products and technologies;
- our ability to establish and maintain commercial manufacturing arrangements for the manufacture of drug product on behalf of third-party pharmaceutical companies; and
- our ability to establish and maintain additional collaborations on favorable terms, particularly marketing and distribution arrangements for oncology product candidates.

Conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data required to obtain regulatory approval and, even if regulatory approval is obtained, achieve product sales of any of our product candidates other than ONIVYDE. In addition, ONIVYDE or any of our other product candidates, if approved, may not achieve commercial success. We began commercializing MM-398 under the brand name ONIVYDE in the United States in the fourth quarter of 2015. If we fail to generate sufficient revenues from the sale of ONIVYDE or the commercialization of any of our product candidates, we will need to continue to rely on additional financing to achieve our business objectives.

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

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances, licensing arrangements and other marketing and distribution arrangements. We do not have any committed external source of funds, other than

under our collaboration with Baxalta for the development and commercialization of ONIVYDE, which is terminable by Baxalta for convenience upon 180 days prior written notice, and under our development, license and supply agreement with Actavis, which is terminable by Actavis for convenience in specified circumstances upon 90 days prior written notice. Other sources of funds may not be available or, if available, may not be available on terms satisfactory to us and could result in significant stockholder dilution.

To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our existing common stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our stockholders. Additional debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends, and these covenants may also require us to attain certain levels of financial performance and we may not be able to do so; any such failure may result in the acceleration of such debt and the foreclosure by our creditors on the collateral we used to secure the debt. The debt issued in a debt financing would also be senior to our outstanding shares of capital stock, and may rank equally with or senior to the convertible notes and the 2022 notes, upon our liquidation. Our existing indebtedness and the pledge of our assets as collateral limit our ability to obtain additional debt financing. If we raise additional funds through marketing and distribution arrangements or other collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish

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valuable rights to our technologies, future revenue streams, research programs or product candidates or to grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

***Our investments are subject to risks that could result in losses.***

We invest our cash in a variety of financial instruments, principally securities issued by the U.S. government and its agencies, investment grade corporate bonds, including commercial paper, and money market instruments. All of these investments are subject to credit, liquidity, market and interest rate risk. Such risks, including the failure or severe financial distress of the financial institutions that hold our cash, cash equivalents and investments, may result in a loss of liquidity, impairment to our investments, realization of substantial future losses, or a complete loss of the investments in the long-term, which may have a material adverse effect on our business, results of operations, liquidity and financial condition. In order to manage the risk to our investments, we maintain an investment policy that, among other things, limits the amount that we may invest in any one issue or any single issuer and requires us to only invest in high credit quality securities.

**Risks Related to the Development and Commercialization of Our Product Candidates**

***We depend heavily on the successful commercialization of ONIVYDE and the success of our clinical stage product candidates. All of our product candidates other than ONIVYDE are still in preclinical and clinical development. Clinical trials of our product candidates may not be successful. If we are unable to successfully commercialize ONIVYDE or our other product candidates, or experience significant delays in doing so, our business will be materially harmed.***

We have invested a significant portion of our efforts and financial resources in the development of ONIVYDE and our other clinical stage product candidates for the treatment of various types of cancer. Although we have obtained FDA and TFDA approval for ONIVYDE in combination with 5-FU and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy in the United States and Taiwan, respectively, all of our product candidates, including MM-398 in additional indications, are still in preclinical and clinical development. Our ability to generate meaningful product revenues will depend heavily on the successful commercialization of ONIVYDE and development of our product candidates. The success of ONIVYDE and other product candidates, which include both our therapeutic product candidates and diagnostic candidates, will depend on several factors, including the following:

- successful enrollment in, and completion of, preclinical studies and clinical trials;
- receipt of marketing approvals from the FDA and similar regulatory authorities outside the United States for our product candidates, including our diagnostics;
- establishing commercial manufacturing capabilities, either by building such facilities ourselves or making arrangements with third-party manufacturers;

launching commercial sales of any approved products, whether alone or in collaboration with others;

acceptance of any approved products by patients, the medical community and third-party payors;

effectively competing with other therapies;

a continued acceptable safety profile of any products following approval; and

qualifying for, maintaining, enforcing and defending intellectual property rights and claims.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize ONIVYDE and our other product candidates, which would materially harm our business.

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***Even though ONIVYDE has been approved for marketing in the United States and Taiwan, we or Baxalta may never receive approval to commercialize ONIVYDE in other parts of the world.***

We have out-licensed the rights for the development and commercialization of ONIVYDE outside of the United States and Taiwan. In order to market our products outside of the United States, we or our collaboration partners must comply with numerous and varying regulatory requirements of other jurisdictions regarding safety and efficacy. Approval procedures vary among jurisdictions and can involve product testing and administrative review periods different from, and greater than, those in the United States. Potential risks include that the regulatory authorities may not:

- deem our products safe and effective;
- find the data from clinical trials sufficient to support approval;
- approve of manufacturing processes and facilities;
- approve our products for any or all indications for which approval is sought.

If ONIVYDE fails to receive marketing approval in other parts of the world, our business may be materially harmed.

***If clinical trials of our product candidates fail to demonstrate safety and efficacy to the satisfaction of the FDA or similar regulatory authorities outside the United States or do not otherwise produce positive results, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.***

Even though ONIVYDE has been approved for marketing in the United States and Taiwan, we may never receive approval to commercialize our other product candidates in the United States or other jurisdictions, or to commercialize MM-398 in other parts of the world. Before obtaining regulatory approval for the sale of our product candidates, we must conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more of our clinical trials can occur at any stage of testing. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and successful interim results of a clinical trial do not necessarily predict successful final results.

We may experience numerous unexpected events during, or as a result of, clinical trials that could delay or prevent our ability to receive regulatory approval or commercialize our product candidates, including:

- regulators or institutional review boards may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;

clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;

the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be insufficient or slower than we anticipate or patients may drop out of these clinical trials 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;

we might have to suspend or terminate clinical trials of our product candidates for various reasons, including a finding of a lack of clinical response or a finding that the patients are being exposed to unacceptable health risks;

regulators or institutional review boards may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements;

the cost of clinical trials of our product candidates may be greater than we anticipate;

the supply or quality of our product candidates, diagnostics or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate; and

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our product candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators to suspend or terminate the trials.

For example, in February 2015, we stopped enrolling patients in our Phase 2 clinical trial of MM-111, a bispecific antibody product candidate, for the treatment of advanced gastric, esophageal and gastroesophageal junction cancers prior to full enrollment based on a recommendation from the Data Safety Monitoring Board for that clinical trial, which cited shorter PFS on the treatment arm relative to the control arm in the overall patient population. We do not plan to invest in additional development of MM-111 at this time. In our previous Phase 2 clinical trial of MM-121 in patients with non-small cell lung cancer, two of the three cohorts (Groups A and C) failed to meet their primary endpoints, and the third cohort (Group B) did not pass its planned interim analysis and ceased enrolling patients. Additionally, we did not meet the primary endpoints in our previous Phase 2 clinical trials of MM-121 in patients with ovarian cancer or in patients with breast cancer, although our ongoing biomarker analysis in each trial identified a potential subpopulation of patients benefiting from MM-121 in combination with either paclitaxel or exemestane, respectively.

Preclinical and clinical data may not be predictive of the success of later clinical trials, and are often susceptible to varying interpretations and analyses. Many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products.

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

be delayed in obtaining marketing approval for our product candidates;

not obtain marketing approval at all;

obtain approval for indications that are not as broad as intended;

have the product removed from the market after obtaining marketing approval;

be subject to additional post-marketing testing requirements;

be subject to restrictions on how the product is distributed or used; or

be unable to obtain reimbursement for use of the product.

Delays in testing or approvals may result in increases to our product development costs. We do not know whether any clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all.

Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to commercialize our product candidates and may harm our business and results of operations.

***If serious adverse or undesirable side effects are identified during the development of our product candidates or following their approval and commercialization, we may need to modify or abandon our development or marketing of such product or product candidate.***

All of our product candidates, other than ONIVYDE in combination with 5-FU and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy, are still in preclinical or clinical development and their risk of failure is high. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive regulatory approval, and it is impossible to ensure that safety or efficacy issues will not arise following regulatory approval. Currently marketed therapies for solid tumors are generally limited to some extent by their toxicity. Use of our product candidates as monotherapies in clinical trials also has resulted in adverse events consistent in nature with other marketed therapies. When used in combination with other marketed or investigational therapies, our product candidates may exacerbate adverse events associated with the other therapy. If our products or product candidates, either alone or in combination with other therapies, result in undesirable side effects or have characteristics that are unexpected, we may need to modify or abandon their development or marketing. For instance, the label for ONIVYDE contains a boxed warning with respect to severe neutropenia and severe diarrhea, which must be clearly conveyed in all marketing materials. Physicians perceptions of the risks conveyed by the ONIVYDE boxed warning could impact their willingness to prescribe ONIVYDE.

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

We may not be able to initiate or continue clinical trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials to obtain a statistically significant result as required by the FDA or other regulatory authorities. In addition, many of our competitors have ongoing clinical trials for product candidates that could be competitive with our product candidates. Patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors product candidates or rely upon treatment with existing therapies that may preclude them from eligibility for our clinical trials.

Enrollment delays in our clinical trials may result in increased development costs for our product candidates, which would cause the value of the company to decline and limit our ability to obtain additional financing. Our inability to enroll a sufficient number of patients for any of our current or future clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether.

In general, we forecast enrollment for our clinical trials based on experience from previous clinical trials and monitor enrollment to be able to make adjustments to clinical trials when appropriate, including as a result of slower than expected enrollment that we experience from time to time in our clinical trials. For example, we experienced slower than expected enrollment in our Phase 2 clinical trial of MM-121 in combination with exemestane for hormone receptor positive breast cancer. In response, we revised the entry criteria for the clinical trial to correspond with changes in clinical practice and also expanded the number of sites and countries participating in the clinical trial. It is possible that slow enrollment in other clinical trials in the future could require us to make similar adjustments. If these adjustments do not overcome problems with slow enrollment, we could experience significant delays or abandon the applicable clinical trial altogether.

***If we are unable to successfully develop diagnostics for our therapeutic product candidates, or experience significant delays in doing so, we may not realize the full commercial potential of our therapeutics.***

An important component of our business strategy is to develop, either alone or together with third parties, *in vitro* or *in vivo* diagnostics for each of our therapeutic product candidates. There has been limited success to date industry-wide in developing diagnostics, in particular *in vitro* diagnostics. To be successful, we will need to address a number of scientific, technical, regulatory and logistical challenges.

Although we have developed prototype assays for some *in vitro* diagnostic candidates, all of our diagnostic candidates are in preclinical development or clinical feasibility testing. We have limited experience in the development of diagnostics and may not be successful in developing appropriate diagnostics to pair with any of our therapeutic product candidates that receive marketing approval. The FDA and similar regulatory authorities outside the United States are generally expected to regulate *in vitro* companion diagnostics as medical devices and *in vivo* companion diagnostics as drugs. In each case, companion diagnostics require separate regulatory approval prior to commercialization. Given our limited experience in developing diagnostics, we expect to rely in part on third parties for their design, development and manufacture. If we, or any third parties that we engage to assist us, are unable to successfully develop diagnostics for our therapeutic product candidates, or experience delays in doing so, the development of our therapeutic product candidates may be adversely affected, our therapeutic product candidates may not receive marketing approval and we may not realize the full commercial potential of any therapeutics that receive marketing approval. As a result, our business would be harmed, possibly materially.

***Any of our product candidates that receive regulatory approval may fail to achieve the degree of market acceptance by physicians, patients, healthcare payors and others in the medical community necessary for commercial success.***

Even though ONIVYDE has received marketing approval, it, or any of our other product candidates that receive marketing approval, may nonetheless not gain sufficient market acceptance by physicians, patients, healthcare payors and others in the medical community. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenues and we may not become profitable. The degree of market acceptance of ONIVYDE and our other product candidates, if approved for commercial sale, will depend on a number of factors that may be uncertain or subjective, including:

- the prevalence and severity of any side effects;

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efficacy and potential advantages or disadvantages compared to alternative treatments;

the price we charge for our product candidates;

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;

our ability to successfully develop diagnostics that effectively identify patient populations likely to benefit from treatment with our therapeutic products;

the strength of marketing and distribution support; and

sufficient third-party coverage or reimbursement.

***If we are unable to effectively educate healthcare professionals or enter into agreements with third parties to sell and market our product, we may not be successful in commercializing ONIVYDE or any other product candidates for which we receive marketing approval.***

ONIVYDE is the first product that we are commercializing. We have no prior experience in the sale, marketing or distribution of therapeutic products. To achieve commercial success for any approved product, we must either build a field organization or outsource this function to third parties. We have established an organization to educate healthcare professionals on ONIVYDE in the United States. We expect that Baxalta and PharmaEngine will market and sell ONIVYDE in the rest of the world in the jurisdictions in which it receives marketing approvals. Our commercialization plans for our other therapeutic candidates will depend in part on any future collaborations into which we may enter.

There are risks involved with both establishing our own commercial capabilities and entering into arrangements with third parties to perform these services. For example, we have a small field force of clinically trained professionals who are charged with educating healthcare professionals about ONIVYDE and Merrimack. This differs from the traditional field model in that it is neither a traditional field sales force nor a traditional medical science liaison role. While we believe that our field strategy will better meet the needs of our customers, this strategy may not be effective.

We also may not be successful entering into arrangements with third parties to sell and market our product candidates or doing so on terms that are favorable to us. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

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

The development and commercialization of new therapeutic and diagnostic products is highly competitive. We face competition with respect to ONIVYDE and our other product candidates, and will face competition with respect to any products that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. Several large pharmaceutical and biotechnology companies currently market and sell products for the treatment of the solid tumor indications for which we are developing our product candidates. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization. Many of these competitors are attempting to develop therapeutics for our target indications.

We are developing our product candidates for the treatment of solid tumors. There are a variety of available therapies marketed for solid tumors. In many cases, these drugs are administered in combination to enhance efficacy. Some of these drugs are branded and subject to patent protection, and others are available on a generic basis, including the active ingredients in ONIVYDE and MM-302. Many of these approved drugs are well established therapies and are widely accepted by physicians, patients and third-party payors. This may make it difficult for us to achieve our business strategy of replacing existing therapies with our product candidates.

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There are also a number of products in late stage clinical development to treat solid tumors. Our competitors may develop products that are more effective, safer, more convenient or less costly than any that we are developing or that would render ONIVYDE or our other product candidates obsolete or non-competitive. Our competitors may also obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours. In addition, our ability to compete may be affected because in many cases insurers or other third-party payors seek to encourage the use of generic products. There are many generic products currently on the market for the indications that we are pursuing, and additional products are expected to become available on a generic basis over the coming years.

Many of our competitors 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. Mergers and acquisitions in the pharmaceutical, biotechnology and diagnostic industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These 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.

***ONIVYDE or any of our product candidates that we successfully commercialize may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, which could harm our business.***

The regulations that govern marketing approvals, pricing and reimbursement for new therapeutic and diagnostic products, including ONIVYDE, 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 or product licensing 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 regulatory approval for a product in a particular country, but then be subject to price regulations that delay our commercial launch of the product and negatively impact the revenues we are able to generate from the sale of the product 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 regulatory approval.

Our ability to commercialize ONIVYDE and any other approved products successfully also will depend in part on the extent to which coverage and reimbursement for these products and related treatments will be available from third-party payors, including government payors such as Medicare and Medicaid, private health insurers and managed care organizations. There have been, and we expect there will continue to be, legislative and regulatory proposals to change the healthcare system in ways that could impact our ability to sell our products profitably. A primary trend in the U.S. healthcare industry and elsewhere is cost containment. The federal government, state legislatures and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid healthcare costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. Adoption of such controls and measures, and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for pharmaceuticals such as ONIVYDE and the other product candidates that we are developing and could have a material adverse effect our net revenue and results.

Third-party payors decide which drugs they will pay for and establish reimbursement and co-pay levels. The growing emphasis on managed care in the United States has increased and we expect will continue to increase the pressure on drug pricing. Third-party payors are increasingly challenging the prices charged for medical products and services and

examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. If these third-party payors do not consider our products to be cost-effective compared to other available therapies, they may not cover our products after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products at a profit. In order to secure coverage and reimbursement for any product that might be approved for sale, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable regulatory approvals. Even with clinical trials, our product candidates may be considered less safe, less effective, of less cost-effective than other products, and third-party payors may not provide coverage and reimbursement for our products or any of our product candidates that we commercialize, in whole or in part.

The process for determining whether a payor will provide coverage for a drug product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the drug product once coverage is approved. Third-party payors may limit coverage to specific drug products on a formulary, which might not include all of the approved drugs for a particular indication, and a payor s decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved.

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We cannot be sure that reimbursement will be available for any product that we commercialize and, if reimbursement is available, what the level of reimbursement will be. Reimbursement may impact the demand for, or the price of, ONIVYDE and any other product for which we obtain marketing approval. Third-party reimbursement may not be sufficient to enable us to maintain price levels high enough to realize an appropriate return on our investment in product development. Obtaining reimbursement for our products may be particularly difficult because of the higher prices often associated with products administered under the supervision of a physician. In addition, coverage policies, third-party reimbursement rates and drug pricing regulation may change at any time. Thus, even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future. The marketability of any products for which we receive regulatory approval for commercial sale may also suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. If reimbursement is not available or is available only to limited levels, we may not be able to successfully commercialize ONIVYDE or any other product candidate that we successfully develop.

We cannot be sure that ONIVYDE will be assigned to a unique HCPCS code that will result in Medicare payment. Presently, HCPCS code J9206 described as Irinotecan Injection exists. If ONIVYDE were to be assigned to this HCPCS code, the payment rate for ONIVYDE would not be based exclusively on its own pricing information but on pricing information for all products assigned to that HCPCS code which, at present, includes both brand name and generic products. This payment rate may be insufficient to enable us to fully realize commercial success.

Payors also are increasingly considering new metrics as the basis for reimbursement rates, such as average sales price, average manufacturer price and actual acquisition cost. The existing data for reimbursement based on these metrics is relatively limited, although certain states have begun to survey acquisition cost data for the purpose of setting Medicaid reimbursement rates. CMS surveys and publishes retail community pharmacy acquisition cost information in the NADAC files to provide state Medicaid agencies with a basis of comparison for their own reimbursement and pricing methodologies and rates. Changes in these reimbursement mechanisms may have a material adverse effect on our revenue.

Moreover, there may be significant delays in obtaining reimbursement for ONIVYDE and any other approved products, and coverage may be more limited than the purposes for which the product is approved by the FDA or regulatory authorities in other countries. Eligibility for reimbursement does not imply that any product will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim payments for new products, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Payment rates may vary according to the use of the product and the clinical setting in which it is used, may be based on payments allowed for lower cost products that are already reimbursed, and may be incorporated into existing payments for other services. Net prices for products may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future weakening of laws that presently restrict imports of products 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 appropriate payment rates from both government-funded and private payors for new products that we develop could therefore have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products, and our overall financial condition.

***Product liability lawsuits against us could cause us to incur substantial liabilities and to limit commercialization of ONIVYDE and any other products that we may develop.***

We face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials and an even greater risk related to the commercial sale of ONIVYDE and any other products that we may develop. If we cannot successfully defend ourselves against claims that ONIVYDE or our other product candidates caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

decreased demand for ONIVYDE or any other products or product candidates that we may develop;

injury to our reputation and significant negative media attention;

withdrawal of patients from clinical trials;

significant costs to defend the related litigation;

substantial monetary awards to patients;

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loss of revenue; and

the inability to commercialize any products that we may develop.

We currently hold $10.0 million in product liability insurance coverage, which may not be adequate to cover all liabilities that we may incur. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any or every liability that may arise.

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

Because we have limited financial and managerial resources, we focus on research programs and product candidates for specific indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products.

We have based our research and development efforts on our systems biology approach to biomedical research. Notwithstanding our large investment to date and anticipated future expenditures in our proprietary approach to research and development, we may fail to address or develop product candidates or indications based on other scientific approaches that may offer greater commercial potential or for which there is a greater likelihood of success.

We also may not be successful in our efforts to identify or discover new or additional product candidates through our systems biology approach. Research programs to identify new product candidates require substantial technical, financial and human resources. These research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development.

If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have otherwise been more advantageous for us to retain sole development and commercialization rights.

***We plan to establish separately funded companies for the development of product candidates using our systems biology approach in some areas outside the oncology field. These companies may not be successful in the development and commercialization of any product candidates.***

We plan to apply our systems biology approach to multiple additional disease areas outside the oncology field. We expect to do so in some cases through the establishment of separately funded companies. For example, we established Silver Creek to research and develop regenerative medicines to repair the heart using our systems biology approach. Silver Creek has received separate funding from investors other than us. Although Silver Creek is currently majority owned by us, in the future we may not be the majority owner of or control Silver Creek or other companies that we establish. If in the future we do not control Silver Creek or any future similar company that we establish, Silver Creek or such other companies could take actions that we do not endorse or with which we disagree, such as using our systems biology approach in a way that reflects adversely on us. In addition, these companies may have difficulty raising additional funds and could encounter any of the risks in developing and commercializing product candidates to which we are subject.

***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 radioactive and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We also store certain low level radioactive waste at our facilities until the materials can be properly disposed of. 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.

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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, use or disposal of biological, hazardous or radioactive materials.

In addition, we may be required to incur substantial costs to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

***Fluctuations in foreign currency exchange rates could substantially increase the costs of our clinical trial programs.***

A significant portion of our clinical trial activities are conducted outside of the United States, and associated costs may be incurred in the local currency of the country in which the trial is being conducted, which costs could be subject to fluctuations in foreign exchange rates. At present, we do not engage in hedging transactions to protect against uncertainty in future exchange rates between particular foreign currencies and the U.S. dollar. A decline in the value of the U.S. dollar against currencies in geographies in which we conduct clinical trials could have a negative impact on our research and development costs. We cannot predict the impact of foreign currency fluctuations, and foreign currency fluctuations in the future may adversely affect our development costs.

**Risks Related to Our Dependence on Third Parties**

***The successful commercialization and continued development of MM-398 depends substantially on our collaboration with Baxalta. If Baxalta is unable or unwilling to commercialize or further develop MM-398, or experiences significant delays in doing so, our business will be materially harmed.***

In September 2014, we entered into a license and collaboration agreement with Baxalta for the development and commercialization of MM-398. Prior to this collaboration, we did not have a history of working with Baxalta. The collaboration involves a complex allocation of rights, provides for milestone payments to us based on the achievement of specified development, regulatory and commercial sale milestones, and provides us with royalty-based revenue if ONIVYDE is successfully commercialized. We cannot predict the success of the collaboration.

Under our license and collaboration agreement, Baxalta has significant control over the conduct and timing of development and commercialization efforts with respect to ONIVYDE outside of the United States. We have little control over the amount, timing and quality of resources that Baxalta devotes to the development or commercialization of ONIVYDE outside of the United States. If Baxalta fails to devote sufficient financial and other resources to the future development or commercialization of ONIVYDE outside of the United States, the development and commercialization of ONIVYDE outside of the United States would be delayed or could fail. This would result in a delay in our receiving milestone payments or royalties with respect to ONIVYDE outside of the United States or in our not receiving such milestone payments or royalties at all.

***If we lose Baxalta as a collaborator in the development or commercialization of ONIVYDE, our business will be materially harmed.***

Baxalta has the right to terminate our agreement for the development and commercialization of ONIVYDE, in whole or with respect to specified territories, at any time and for any reason, upon 180 days prior written notice. Baxalta also

has the right to terminate our agreement if we fail to cure a material breach of our agreement within a specified cure period, or fail to diligently pursue a cure if such a breach is not curable within such period.

If Baxalta terminates our agreement at any time, whether on the basis of our uncured material breach or for any other reason, it would delay or prevent our further development of MM-398 and materially harm our business and could accelerate our need for additional capital. In particular, we would have to fund the future clinical development and commercialization of ONIVYDE outside of the United States on our own, seek another collaborator or licensee for such clinical development and commercialization, or abandon the future clinical development and commercialization of ONIVYDE outside of the United States.

Additionally, if Baxalta undergoes a change in control or management, this may adversely affect our collaborative relationship or the commercialization of ONIVYDE in the partnered territories. Such a change in control may result in a reprioritization of ONIVYDE within Baxalta s portfolio, or Baxalta failing to maintain the financial or other resources necessary to continue supporting its commercialization of ONIVYDE.

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***We may depend on collaborations with third parties for the development and commercialization of our product candidates. If those collaborations are not successful, we may not be able to capitalize on the market potential of these product candidates.***

Depending on our capital requirements, development and commercialization costs, need for additional therapeutic expertise and other factors, it is possible that we will enter into additional development and commercialization arrangements with respect to either oncology product candidates or product candidates in other therapeutic areas. In particular, while we expect to apply our systems biology approach to other disease areas through arrangements similar to Silver Creek, it is also possible that we will seek to enter into licensing agreements or other types of collaborations for the application of our systems biology approach.

Our likely collaborators for any distribution, marketing, licensing or broader collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. We will have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on our collaborators abilities to successfully perform the functions assigned to them in these arrangements.

Collaborations involving our product candidates, including our collaboration with Baxalta, 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 not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in their strategic focus or available funding, or external factors such as an acquisition that diverts resources or creates competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or 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 if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive;
- a collaborator with marketing and distribution rights to one or more products may not commit sufficient resources to their marketing and distribution;

collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our proprietary information or expose us to potential litigation;

disputes may arise between us and the collaborators that result in the delay or termination of the research, development or commercialization of our product candidates or that result in costly litigation or arbitration that diverts management attention and resources; and

collaborations may be terminated, such as the termination of our license and collaboration agreement with Sanofi effective December 17, 2014, and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. 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. 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 could be delayed, diminished or terminated.

***If we are not able to establish additional collaborations, we may have to alter our development plans.***

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

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We face significant competition in seeking appropriate collaborators. Collaborations are complex and time-consuming to negotiate and document. We may also be restricted under existing collaboration agreements from entering into agreements on certain terms with other potential collaborators. We may not be able to negotiate collaborations on acceptable terms, or at all. If that were to occur, we may have to curtail the development of a particular product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of our 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 will not be able to bring our product candidates to market and generate product revenue.

***We rely on third parties to conduct our clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials.***

We do not independently conduct clinical trials of our product candidates. We rely on third parties, such as contract research organizations, clinical data management organizations, medical institutions and clinical investigators, to perform this function. Our reliance on these third parties for clinical development activities reduces our control over these activities but does not relieve us of our responsibilities. We remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA and other international regulatory agencies require us to comply with standards, commonly referred to as good clinical practices, for conducting, recording and reporting the results of clinical trials to assure that adverse event data are reported within required timeframes, that data and reported results are credible and accurate and that the rights, integrity and confidentiality of patients in clinical trials are protected. Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, regulatory approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates.

We also rely on other third parties to store and distribute supplies for our clinical trials. Any performance failure on the part of our existing or future distributors could delay clinical development or regulatory approval of our product candidates or commercialization of our products or cause us to incur additional costs, producing additional losses and depriving us of potential product revenue.

We also intend to utilize diagnostics in several of our current and planned clinical trials, including current clinical trials of MM-121 and MM-141, to preselect patients who will receive specified treatment regimens. We will rely on third-party laboratories to test patient samples in connection with such diagnostics. Any failure on the part of these laboratories to properly perform such testing could jeopardize those clinical trials and delay or prevent the approval of the associated therapeutic candidate.

**Risks Related to the Manufacturing of Our Product Candidates**

***We have limited experience in manufacturing our product candidates. We will need to upgrade and expand our manufacturing facility and augment our manufacturing personnel and processes in order to meet our business plans. If we fail to do so, we may not have sufficient drug product to meet our clinical development and commercial requirements.***

We have a manufacturing facility located at our corporate headquarters in Cambridge, Massachusetts. We manufacture drug substance at this facility that we use for commercial sales of ONIVYDE, research and development purposes and for clinical trials of our product candidates. We have limited experience in manufacturing products at a commercial scale. Our current facility may not be sufficient to permit expanded manufacture of ONIVYDE or our other product candidates for Phase 3 clinical trials or commercial sale. In order to meet our business plan, which contemplates our internally manufacturing drug substance for most of our clinical trials for all or a significant portion of our commercial requirements, we will need to upgrade and expand our manufacturing facilities, add manufacturing personnel and ensure that validated processes are consistently implemented in our facilities. The upgrade and expansion of our facilities will require additional regulatory approvals. In addition, it will be costly and time-consuming to expand our facilities and recruit necessary additional personnel. If we are unable to expand our facilities in compliance with regulatory requirements or to hire additional necessary manufacturing personnel, we may encounter delays or additional costs in achieving our research, development and commercialization objectives, including in obtaining regulatory approvals of our product candidates, which could materially damage our business and financial position.

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***If our manufacturing facility is damaged or destroyed or production at this facility is otherwise interrupted, our business and prospects would be negatively affected and our commercialization efforts may be materially harmed.***

If the manufacturing facility at our corporate headquarters or the equipment in it is damaged or destroyed, we may not be able to quickly or economically replace our manufacturing capacity or replace it at all. If such an event occurs, the supply of ONIVYDE and our other product candidates would be interrupted. In the event of a temporary or protracted loss of this facility or equipment, we might not be able to transfer manufacturing to a third party and could lose potential revenue from the sales of ONIVYDE and any other products for which we obtain regulatory approval. Even if we could transfer manufacturing to a third party, the shift would likely be expensive and time-consuming, particularly since the new facility would need to comply with the necessary regulatory requirements and we would need FDA approval before selling ONIVYDE or any other products manufactured at that facility. Such an event could delay our clinical trials or reduce our product sales of ONIVYDE and any other products that are approved by the FDA.

Currently, we maintain insurance coverage against damage to our property and equipment and to cover business interruption and research and development restoration expenses. If we have underestimated our insurance needs with respect to an interruption in our clinical manufacturing of our product candidates, we may not be able to cover our losses.

Any other interruption of production at our manufacturing facility also could damage our business. For example, in 2009, we experienced a viral contamination at this facility that required that we shut the facility entirely for decontamination. Because of this contamination, the FDA placed a partial clinical hold on our IND for MM-121 until we submitted supporting documentation to the FDA regarding our decontamination procedures. Although we were able to resolve this issue, with the FDA lifting the partial clinical hold in April 2010, other companies have experienced similar contamination problems, and we could experience a similar problem in the future that is more difficult to resolve.

***We expect to continue to contract with third parties for at least some aspects of the production of ONIVYDE and our other product candidates for commercial sale and clinical trials. This increases the risk that we will not have sufficient quantities of ONIVYDE or our other product candidates at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.***

We currently rely on third-party manufacturers for some aspects of the production of ONIVYDE and our other product candidates, including the production of MM-121 and fill-finish and labeling activities for ONIVYDE and our other product candidates. In addition, while we believe that our existing manufacturing facility or additional facilities that we build will be sufficient to meet our requirements for manufacturing a significant portion of drug substance for our research and development activities, we may need to rely on third-party manufacturers for some of these requirements, particularly later stage clinical trials of our antibody product candidates, and, at least in the near term, for commercial supply of ONIVYDE and any other products for which we obtain marketing approval.

In connection with the termination of our license and collaboration agreement with Sanofi for the development and commercialization of MM-121 in 2014, we assumed an agreement with a third-party manufacturer for the manufacture of MM-121. We do not have any other agreements with third-party manufacturers for the clinical supply to us of MM-398 or commercial supply to us of ONIVYDE or any other product candidates, and we may be unable to conclude such agreements or to do so on acceptable terms. Reliance on third-party manufacturers entails additional risks, including:

reliance on the third party for regulatory compliance and quality assurance;

the possible breach of the manufacturing agreement by the third party; and

the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

Third-party manufacturers may not be able to comply with cGMP, QSR or similar regulatory requirements outside the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations 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 products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our products.

Any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. Because there are a limited number of manufacturers that operate under cGMP or QSR regulations and that might be capable of manufacturing for us, we may not have access to such manufacturers.

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We currently rely on single suppliers for the resins, media and filters that we use for our manufacturing process. We purchase these materials from our suppliers on a purchase order basis and do not have long-term supply agreements in place. Any performance failure or refusal to supply on the part of our existing or future suppliers could delay clinical development, marketing approval or commercialization of our products. If our current suppliers cannot perform as agreed, we may be required to replace one or more of these suppliers. Although we believe that there may be a number of potential long-term replacements to each supplier, we may incur added costs and delays in identifying and qualifying any such replacements.

We likely will rely upon third-party manufacturers to provide us with necessary reagents and instruments to develop, test and manufacture our *in vitro* diagnostics. Currently, many reagents are marketed as Research Use Only products under FDA regulations.

Our potential future dependence upon others for the manufacture of our product candidates may adversely affect our future profit margins and our ability to commercialize any products that receive regulatory approval on a timely and competitive basis.

***We rely on third parties to perform various tasks related to the manufacturing of our product candidates. Compliance by such third parties with regulations of the FDA or other regulatory bodies cannot be assured, which could adversely impact our ability to supply our product candidates.***

Although we perform much of the bulk manufacturing for ONIVYDE and our other product candidates, we rely on third parties to perform the fill-finish and packaging steps. If any of those third parties were to fail to be in compliance with regulations of the FDA or other regulatory bodies, our ability to supply ONIVYDE and our other product candidates could be adversely impacted.

For instance, in 2010, a former fill-finish third-party contractor that we used to fill and package MM-121 experienced FDA inspection issues with its quality control processes that resulted in a formal warning letter from the FDA. As a result, we pulled some MM-121 from clinical trial sites and replaced it with MM-121 that was filled by a different contractor. This restocking resulted in a few patients missing one or two doses of MM-121. It is possible that we could experience similar issues with other contractors.

**Risks Related to Our Intellectual Property**

***If we fail to fulfill our obligations under our intellectual property licenses with third parties, we could lose license rights that are important to our business.***

We are a party to a number of intellectual property license agreements with third parties, including with respect to MM-302, MM-121, MM-141 and MM-151, and expect to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that our future license agreements will impose, various diligence, milestone payment, royalty, insurance and other obligations on us. If we fail to comply with these obligations, our licensors may have the right to terminate these agreements, in which event we might not be able to develop and market any product that is covered by these agreements. Termination of these licenses or reduction or elimination of our licensed rights may result in our having to negotiate new or reinstated licenses with less favorable terms. The occurrence of such events could materially harm our business.

***If we are unable to obtain and maintain patent protection for our technology and products, or if our licensors are unable to obtain and maintain patent protection for the technology or products that we license from them, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability***

***to successfully commercialize our technology and products may be adversely affected.***

Our success depends in large part on our and our licensors ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary technology and products. In some circumstances, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology or products that we license from third parties. Therefore, we cannot be certain that these patents and applications will be prosecuted and enforced in a manner consistent with the best interests of our business. In addition, if third parties who license patents to us fail to maintain such patents, or lose rights to those patents, the rights we have licensed may be reduced or eliminated.

We have sought to protect our proprietary position by filing patent applications in the United States and abroad related to our novel technologies and products that are important to our business. This process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. 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.

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The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our and our licensors patent rights are highly uncertain. Our and our licensors pending and future patent applications may not result in patents being issued that protect our technology or products or that effectively prevent others from commercializing competitive technologies and products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. The laws of foreign countries may not protect our rights to the same extent as the laws of the United States. 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 be certain that we or our licensors were the first to make the inventions claimed in our owned and licensed patents or pending patent applications, or that we or our licensors were the first to file for patent protection of such inventions. Assuming the other requirements for patentability are met, the first to file a patent application is entitled to the patent. Under the America Invents Act enacted in 2011, the United States moved to this first to file system in early 2013 from the previous system under which the first to make the claimed invention was entitled to the patent. We may become involved in opposition, interference or derivation proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such proceeding could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights.

Even if our owned and licensed patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner. The issuance of a patent is not conclusive as to its scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in patent claims being narrowed, invalidated or held unenforceable, which could limit our ability to stop or prevent us from stopping others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. 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 owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

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

Competitors may infringe our patents. To counter infringement or unauthorized use, we may be required to initiate infringement lawsuits, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly. 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.

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

Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the enforceable proprietary rights of third parties. We may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our products and technology, including interference or derivation proceedings before the U.S. Patent and Trademark Office. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. If we are found to infringe a third party s intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our 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. In addition, we could be found liable for monetary damages. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties can have a similar negative impact on our business.

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***We may be subject to claims that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.***

Many of our employees were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees 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 employees have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee s former employer. Litigation may be necessary to defend against these claims. If we fail in 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 defending against such claims, litigation could result in substantial costs and be a distraction to management.

***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 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 our resources available for development activities. We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their substantially greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

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

In addition to our patented technology and products, we rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties that have access to them, such as our employees, corporate collaborators, outside scientific collaborators, sponsored researchers, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. In addition, any of these parties may breach the agreements and disclose our proprietary information, and we may not be able to obtain adequate remedies for such breaches. 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, 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, our competitive position would be harmed.

***We may not be able to obtain, maintain or protect proprietary rights necessary for the continued development and commercialization of our products, product candidates and research technologies, including as a result of challenges from companies who seek to sell generic versions of ONIVYDE after expiration of our orphan drug exclusivity but prior to our ONIVYDE patent expiration.***

Our commercial success depends in large part on obtaining and maintaining U.S. and foreign patent protection for our products, our product candidates and our research technologies and successfully enforcing and defending these patents against third-party challenges, including with respect to generic challenges. The validity of our patents in one or more jurisdictions may be challenged by third parties, resulting in our patents being deemed invalid, unenforceable or narrowed in scope, which could compromise the scope or duration of our exclusive rights in the relevant product, product candidate or technology. For example, the validity of a U.S. patent can be challenged in the U.S. Patent and Trademark Office (e.g., through an Inter Partes Review and/or Post Grant Review Proceeding) and/or in U.S. federal district court.

In addition, our patents on ONIVYDE may also be challenged in a federal court in connection with a third party s ANDA or a Section 505(b)(2) NDA seeking FDA approval to market a generic version of ONIVYDE, resulting in a patent challenge to one or more patents listed in the Orange Book for ONIVYDE. This patent challenge can result in one or more of those Orange Book patents for ONIVYDE being deemed uninfringed, invalid, unenforceable and/or narrowed in scope, which could compromise the scope or duration of our exclusive rights in the relevant product. An ANDA or Section 505(b)(2) NDA can be filed at any time after FDA approval of ONIVYDE. Other challenges to a patent may be mounted without regard to the date of an FDA approval.

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Our patents as issued or as subsequently limited by any litigation might not contain claims that are sufficiently broad to prevent others from circumventing our patent protection and utilizing our technologies. For instance, the issued patents relating to ONIVYDE and our product candidates may be limited to a particular indication and/or composition and may not cover similar compositions that have similar clinical properties. Consequently, our competitors may independently develop competing products that do not infringe our patents or other intellectual property. Also, our pending patent applications may not issue, and we may not receive any additional patents. We cannot be sure that our patents and patent applications, including our own and those that we have rights to under licenses from third parties, will adequately protect our intellectual property for a number of reasons, including, among other things, the following: (i) the patent positions of pharmaceutical and biotechnology companies can be highly uncertain and involve complex legal and factual questions; (ii) the actual protection afforded by a patent can vary from country to country and may depend upon the type of patent, the scope of its coverage and the availability of legal remedies in the country; (iii) the laws of foreign countries in which we market our products may afford little or no effective protection to our intellectual property, thereby easing our competitors ability to compete with us in such countries; (iv) intellectual property laws and regulations and legal standards relating to the validity, scope and enforcement of patents covering pharmaceutical and biotechnological inventions are continually developing and changing, both in the United States and in other important markets outside the United States (v) third parties may challenge, infringe, circumvent or seek to invalidate existing or future patents owned by or licensed to us; and (vi) the coverage claimed in a patent application can be significantly reduced before the patent is issued, and, as a consequence, our and our partners patent applications may result in patents with narrower coverage than we desire or have planned for.

**Risks Related to Regulatory Approval of Our Product Candidates**

***If we are not able to obtain required regulatory approvals, we will not be able to commercialize our product candidates, and our ability to generate revenue will be materially impaired.***

Our product candidates, including our clinical stage product candidates, 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, import, export, sampling and marketing are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by comparable authorities in other countries. Failure to obtain regulatory approval for a product candidate will prevent us from commercializing the product candidate. On October 22, 2015, we received approval from the FDA and the TFDA to market ONIVYDE in combination with 5-FU and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy in the United States and Taiwan, respectively, which is our first and only product candidate to receive regulatory approval. We have not received regulatory approval to market ONIVYDE in any jurisdiction other than the United States and Taiwan or for any other indications. We have only limited experience in filing and supporting the applications necessary to gain regulatory approvals and expect to rely on third-party contract research organizations to assist us in this process. Securing regulatory approval requires the submission of extensive preclinical and clinical data and supporting information to the FDA and other regulatory agencies 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 FDA or other regulatory agencies. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining regulatory approval or prevent or limit commercial use.

The process of obtaining regulatory approvals is expensive, may take many years if additional clinical trials are required, if approval is obtained at all, and can vary substantially based on a variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in regulatory approval policies during the

development period, changes in or the enactment of additional statutes or regulations, changes in regulatory review for each submitted product application or approval of other products for the same indication may cause delays in the approval or rejection of an application. Regulatory agencies have substantial discretion in the approval process and may refuse to accept any application or may decide that our data is 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 regulatory approval of a product candidate. Any regulatory approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

***If we pursue development of a diagnostic to identify patients who are likely to benefit from a therapeutic product, failure to obtain approval for the diagnostic may prevent or delay approval of the therapeutic product.***

We are attempting to develop diagnostics to identify patients who are likely to benefit from our therapeutic product candidates. We currently rely on and expect to continue to rely on third parties for much of the development, testing and manufacturing of our diagnostics. We will likely rely on such third parties to also obtain any required regulatory approval for and then

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commercially supply such diagnostics. All of our diagnostic candidates are in preclinical development or clinical feasibility testing. We have very limited experience in the development of diagnostics and, even with the help of third parties with greater experience, may fail to obtain the required diagnostic product marketing approval, which could prevent or delay approval of the therapeutic product.

In July 2014, the FDA issued final guidance that stated that if safe and effective use of a therapeutic depends on an *in vitro* diagnostic, then the FDA generally will not approve the therapeutic unless the FDA approves or clears this *in vitro* companion diagnostic device at the same time that the FDA approves the therapeutic. The approval or clearance of the *in vitro* diagnostic most likely will occur through the FDA s Center for Devices and Radiological Health Office of In Vitro Diagnostics and Radiological Health. Even with the issuance of the final guidance, the FDA s expectations for *in vitro* companion diagnostics remain unclear in some respects. The FDA s developing expectations will affect our *in vitro* diagnostics. In particular, the FDA may limit our ability to use retrospective data, otherwise disagree with our approaches to trial design, biomarker qualification, clinical and analytical validity and clinical utility, or make us repeat aspects of the trial or initiate new trials.

Because our diagnostic candidates are at an early stage of development, we cannot yet know what the FDA will require for any of these tests. For several of our clinical stage product candidates, namely MM-121, MM-141 and MM-151, we are attempting to develop an *in vitro* diagnostic that will help identify patients likely to benefit from the therapy. Whether the FDA will consider these *in vitro* diagnostics to be *in vitro* companion diagnostic devices that require simultaneous approval or clearance with the therapeutics will depend on whether the FDA views the diagnostics to be essential to the safety and efficacy of these therapeutics.

Based on the FDA s past practice with companion diagnostics, if we are successful in developing a diagnostic for any of our clinical stage product candidates, we would expect that FDA approval of an *in vitro* companion diagnostic, and possibly an *in vivo* companion diagnostic, would be required for approval and subsequent commercialization of each such therapeutic product candidate. We are not aware of any currently available diagnostics that, if necessary, would otherwise allow us to proceed with the approval and subsequent commercialization of our product candidates despite a delay in or failure of our attempts to develop diagnostics.

For MM-398 and MM-302, although we are also investigating possible *in vitro* diagnostics, we are currently developing *in vivo* diagnostics in the form of imaging agents that may help identify patients more likely to benefit from the therapy. Imaging agents for diagnostic use can be regulated as drugs by the FDA s Center for Drug Evaluation and Research and, as such, would be generally subject to the regulatory requirements applicable to other new drug candidates. Alternatively, several *in vivo* imaging agents have been regulated as medical devices by FDA s Center for Devices and Radiological Health. Although the FDA has not issued guidance with respect to the simultaneous approval of *in vivo* diagnostics and therapeutics, it is possible that the FDA will apply a standard similar to that for *in vitro* diagnostics.

Because we expect to rely on third parties for various aspects of the development, testing and manufacture, as well as for regulatory approval for and commercial supply, of our diagnostics, the commercial success of any of our product candidates that require a diagnostic will be tied to and dependent on the continued ability of such third parties to make the diagnostic commercially available on reasonable terms in the relevant geographies.

***If we fail to maintain orphan drug exclusivity or designation for ONIVYDE or MM-141, we will have to rely on other rights and protections for these product candidates.***

We have obtained orphan drug exclusivity in the United States for ONIVYDE for the treatment of pancreatic cancer and orphan medicinal product designation in the European Union for MM-398 for the treatment of pancreatic cancer.

In addition, we have obtained orphan drug designation in the United States for MM-141 for the treatment of pancreatic cancer. In the United States, under the Orphan Drug Act, the FDA may designate a product 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 in the United States.

In the United States, the company that first obtains FDA approval for a designated orphan drug for the specified rare disease or condition receives orphan drug marketing exclusivity for that drug for that indication for a period of seven years. This orphan drug exclusivity prevents the FDA from approving another application, including a full NDA, to market the same drug for the same orphan indication, except in limited circumstances. For purposes of small molecule drugs, the FDA defines the term same drug to mean a drug that contains the same active molecule and that is intended for the same use as the approved orphan drug. Orphan drug exclusivity may be lost if the FDA 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.

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Even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs can be approved for the same condition. Even after an orphan drug is approved, the FDA can subsequently approve the same drug for the same condition if the FDA concludes that the later drug is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care.

The EMA grants orphan medicinal product designation to promote the development of products that may offer therapeutic benefits for life-threatening or chronically debilitating conditions affecting not more than five in 10,000 people in the European Union. Orphan medicinal product designation from the EMA provides ten years of marketing exclusivity following drug approval, subject to reduction to six years if the designation criteria are no longer met.

***Our therapeutic product candidates for which we intend to seek approval as biological or drug products may face competition sooner than expected.***

With the enactment of the BPCIA as part of the Health Care and Education Reconciliation Act of 2010, or the Health Care Reform Law, an abbreviated pathway for the approval of biosimilar and interchangeable biological products was created. The abbreviated regulatory pathway establishes legal authority for the FDA to review and approve biosimilar biologics, including the possible designation of a biosimilar as interchangeable based on their similarity to existing brand product. Under the BPCIA, an application for a biosimilar product cannot be approved by the FDA until 12 years after the original branded product was approved under a BLA. The BPCIA is complex and has yet to be fully interpreted and implemented by the FDA. As a result, its ultimate impact, implementation and meaning is subject to uncertainty. While it is uncertain when any such processes may be fully adopted by the FDA, any such processes could have a material adverse effect on the future commercial prospects for our biological products.

We believe that any of our products approved as a biological product under a BLA should qualify for the 12 year period of exclusivity. However:

- a potential competitor could seek and obtain approval of its own BLA during our exclusivity period instead of seeking approval of a biosimilar version; and

- the FDA could consider a particular product candidate which contains both drug and biological product components to be a drug subject to review pursuant to an NDA, and therefore eligible for a significantly shorter marketing exclusivity period as provided under the Drug Price Competition and Patent Term Restoration Act of 1984.

Moreover, the extent to which a biosimilar, once approved, will be substituted for any one of our reference products in a way that is similar to traditional generic substitution for non-biological products is not yet clear and will depend on a number of marketplace and regulatory factors that are still developing.

In addition, a drug product approved under an NDA, such as ONIVYDE, could face generic competition earlier than expected. The enactment of the Generic Drug User Fee Amendments of 2012 as part of the FDASIA established a user fee program that will generate hundreds of millions of dollars in funding for the FDA s generic drug review program. Funding from the user fee program, along with performance goals that the FDA negotiated with the generic drug industry, could significantly decrease the timeframe for FDA review and approval of generic drug applications.

***Failure to obtain regulatory approval in international jurisdictions would prevent us from marketing our products abroad.***

We intend to market our products, including ONIVYDE, either ourselves or with commercialization partners, both within and outside the United States. This may increase the risks described below with respect to our compliance with foreign regulations.

In order to market and sell ONIVYDE and our other products in the European Union and many other jurisdictions, we or our commercialization partners must obtain separate regulatory approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing, including sometimes additional testing in children. The time required to obtain approval in foreign countries may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be sold in that country. We or our commercialization partners may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. We or our commercialization partners may not be able to file for regulatory approvals and may not receive necessary approvals to commercialize our products in any market.

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***Any product for which we obtain marketing approval could be subject to restrictions or withdrawal from the market and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products, when and if any of them are approved.***

ONIVYDE and any other product for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such product, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP or QSR requirements relating to quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping. Even if regulatory approval of a product is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the product. Later discovery of previously unknown problems with our products, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in actions such as:

restrictions on such products, manufacturers or manufacturing processes;

restrictions on the marketing of a product;

restrictions on product distribution;

requirements to conduct post-marketing clinical trials;

warning or untitled letters;

withdrawal of the products from the market;

refusal to approve pending applications or supplements to approved applications that we submit;

recall of products;

fines, restitution or disgorgement of profits or revenue;

suspension or withdrawal of regulatory approvals;

refusal to permit the import or export of our products;

product seizure; or

injunctions or the imposition of civil or criminal penalties.

The FDASIA provides the FDA with new inspection authorities. A drug or biologic will be considered adulterated, with possible resulting civil and criminal penalties, if the owner or operator of the establishment where it is made, processed, packed or held delays, denies, limits or refuses inspection. The FDASIA also replaces the biennial inspection schedule for drugs and biologics with a risk-based inspection schedule. The law grants the FDA authority to require a drug or biologics manufacturer to provide, in advance or instead of an inspection, and at the manufacturer s expense, any records or other information that the agency may otherwise inspect at the facility. The FDASIA also permits the FDA to share inspection information with foreign governments under certain circumstances. The FDASIA is complex and has yet to be fully interpreted and implemented by the FDA. As a result, its ultimate impact, implementation and meaning are subject to uncertainty.

The FDASIA also provides the FDA with additional authority to exercise against manufacturers of drugs or biologics that are not adhering to pediatric study requirements, which apply even if the manufacturer is not seeking to market the drug or biologic to pediatric patients. As of April 2013, the FDA must issue non-compliance letters to companies who do not meet the pediatric study requirements. Any company receiving a non-compliance letter would have an opportunity to respond, and the non-compliance letter and company response would become publicly available.

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***Future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and affect the prices we may obtain.***

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any products for which we obtain marketing approval.

For example, in March 2010, President Obama signed into law the Health Care Reform Laws, which were intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, provide benefits for patients within a coverage gap in the Medicare Part D prescription drug program, implement rules regarding prescription drug benefits under the health insurance exchanges and changes to the Medicare Drug Rebate program, expand the PHS 340B drug pricing discount program, enhance remedies against fraud and abuse, add new transparency requirements for healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. These changes impact existing government healthcare programs and are resulting in the development of new programs, including Medicare payment for performance initiatives and improvements to the physician quality reporting system and feedback program. Further, the Health Care Reform Laws impose a significant annual fee on companies that manufacture or import branded prescription drug products. Substantial new provisions affecting compliance have also been enacted, which may affect our business practices with healthcare practitioners. In addition, effective October 1, 2010, the Health Care Reform Laws revised the definition of average manufacturer price for reporting purposes, which could increase the amount of Medicaid drug rebates to states.

Some states have elected not to expand their Medicaid programs by raising the income limit to 133% of the federal poverty level, as is permitted under the Health Care Reform Laws. For each state that does not choose to expand its Medicaid program, there may be fewer insured patients overall, which could impact our sales, business and financial condition. Where Medicaid patients receive insurance coverage under any of the new options made available through the Health Care Reform Laws, the possibility exists that manufacturers may be required to pay Medicaid rebates on drugs used under these circumstances, a decision that could impact manufacturer revenues. In addition, the federal government has also announced delays in the implementation of key provisions of the Health Care Reform Laws, including the employer mandate. The implications of these delays for our sales, business and financial condition, if any, are not yet clear.

The Health Care Reform Laws appear likely to continue the pressure on pharmaceutical pricing, especially under the Medicare program, and may also increase our regulatory burdens and operating costs. Moreover, legislative changes to the Health Care Reform Laws remain possible. We expect that the Health Care Reform Laws, as currently enacted or as it may be amended in the future, and other healthcare reform measures that may be adopted in the future, could have a material adverse effect on our industry generally and on our ability to maintain or increase sales of our existing products or to successfully commercialize our product candidates.

***If we fail to comply with our reporting and payment obligations under U.S. governmental pricing programs, we could be required to reimburse government programs for underpayments and could pay penalties, sanctions and fines which could have a material adverse effect on our business, financial condition and results of operations.***

As a condition of reimbursement for ONIVYDE and any other product approved by the FDA, various U.S. federal and state healthcare programs require that we calculate and report certain pricing information to U.S. federal and state healthcare agencies. For example, we are required to provide average selling price information to CMS on a quarterly basis in order to compute Medicare Part B payment rates. Price reporting and payment obligations are highly complex

and vary among products and programs. The calculation of average selling price includes a number of inputs from contracts with wholesalers, specialty distributors, group purchasing organizations and other customers. We are also required to make an assessment of whether these agreements are deemed to be for bona fide services and that the services are deemed to be at fair market value in our industry and for our products. Our processes for estimating amounts due under these governmental pricing programs involve subjective decisions. As a result, our price reporting calculations are subject to the risk of errors and our methodologies for calculating these prices could be challenged under the federal False Claims Act or other laws. In addition, the Health Care Reform Laws modified the rules related to certain price reports and expanded the scope of pharmaceutical product sales to which Medicaid rebates apply, among other things. Uncertainty exists currently, as many of the specific determinations necessary to implement this new legislation have yet to be decided and communicated to industry participants. This uncertainty in the interpretation of the legislation increases the chances of an error in price reporting, which could in turn lead to a legal challenge, restatement or investigation. If we become subject to investigations, restatements or other inquiries concerning our compliance with price reporting laws and regulations, we could be required to pay or be subject to additional reimbursements, penalties, sanctions or fines, which could have a material adverse effect on our business, financial condition and results of operations.

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We participate in and have certain price reporting obligations to the Medicaid Drug Rebate program and other governmental pricing programs, and we have obligations to report average sales price under the Medicare program. Pricing and rebate calculations vary among products and programs. The calculations are complex and are often subject to interpretation by governmental or regulatory agencies and the courts. For example, the Medicaid rebate amount is computed each quarter based on our submission to the CMS of our AMP and best price for the quarter. If we become aware that our reporting for prior quarters was incorrect, or has changed as a result of recalculation of the pricing data, we will be obligated to resubmit the corrected data for a period not to exceed twelve quarters from the quarter in which the data originally were due. Such restatements and recalculations would serve to increase our costs for complying with the laws and regulations governing the Medicaid rebate program. Any corrections to our rebate calculations could result in an overage or underage in our rebate liability for past quarters, depending on the nature of the correction. Price recalculations also may affect the price that we will be required to charge certain safety net providers under the PHS 340B drug discount program.

We are liable for errors associated with our submission of pricing data and for overcharging government payers. For example, in addition to retroactive rebates and the potential for 340B program refunds, if we are found to have knowingly submitted false AMP or best price information to the government, we may be liable for civil monetary penalties in the amount of $100,000 per item of false information. Our failure to submit monthly/quarterly AMP and best price data on a timely basis could result in a civil monetary penalty of $10,000 per day for each day the submission is late beyond the due date. In the event that CMS were to terminate our rebate agreement, no federal payments would be available under Medicaid or Medicare Part B for our products. In addition, if we overcharge the government in connection with our FSS contract or under any other government program, we will be required to refund the difference to the government. Failure to make necessary disclosures and/or to identify contract overcharges could result in allegations against us under the federal civil false claims act and other laws and regulations.

CMS and the Office of Inspector General of the U.S. Department of Health and Human Services have pursued manufacturers that were alleged to have failed to report these data to the government in a timely manner. Governmental agencies may also make changes in program interpretations, requirements or conditions of participation, some of which may have implications for amounts previously estimated or paid. We cannot assure you that our submissions will not be found by CMS to be incomplete or incorrect.

If we overcharge the government in connection with our FSS contract or the Tricare retail pharmacy program, whether due to a misstated FCP or otherwise, we would be required to refund the difference to the government. Failure to make necessary disclosures and/or to identify contract overcharges can result in allegations against us under the false claims act and other laws and regulations.

Unexpected refunds to the federal government, and responding to a government investigation or enforcement action, would be expensive and time-consuming, and could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

**Risks Related to Commercialization of Our Product Candidates**

***The FDA and other regulatory agencies strictly regulate the promotional claims that may be made about prescription products. If we are found to have improperly promoted off-label uses, we may become subject to significant fines and other liability.***

The FDA and other regulatory agencies strictly regulate the promotional claims that may be made about prescription products. In particular, a product may not be promoted for uses that are not approved by the FDA or such other regulatory agencies as reflected in the product s approved labeling. ONIVYDE is only approved by the FDA and the

TFDA for use in combination with 5-FU and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy in the United States and Taiwan, respectively, and we may only promote ONIVYDE for such use. If we are found to have promoted for off-label uses, we may become subject to significant government fines and other related liability. For example, the U.S. government has levied large civil and criminal fines against companies for alleged improper promotion and has enjoined several companies from engaging in off-label promotion. The government has also required companies to enter into complex multi-year corporate integrity agreements and/or non-prosecution agreements that can impose significant restrictions and other burdens on the affected companies.

In addition, incentives under applicable U.S. laws encourage employees and physicians to report violations of rules governing promotional activities for pharmaceutical products. These incentives could lead to so called whistleblower lawsuits as part of which such persons seek to collect a portion of moneys allegedly overbilled to government agencies due to, for example, promotion of pharmaceutical products beyond labeled claims. Such lawsuits, whether with or without merit, are typically time consuming and costly to defend. Such suits may also result in related stockholder lawsuits, which are also costly to defend.

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

Healthcare providers, physicians and others play a primary role in the recommendation and prescription of ONIVYDE and any other products for which we obtain marketing approval. Our future arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute ONIVYDE and any other products for which we obtain marketing approval. Restrictions under applicable federal, state and foreign healthcare laws and regulations include the following:

- the federal healthcare anti-kickback statute prohibits, among other things, knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward the purchasing, leasing, ordering or arranging for the purchase, order or recommendation of any item or service reimbursable under Medicare, Medicaid, or other federal healthcare programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers on the other, and violations are punishable by imprisonment, criminal fines, civil monetary penalties and exclusion from participation in federal healthcare programs. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution or other regulatory sanctions, the exemptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor;

- the federal False Claims Act prohibits any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government, or knowingly making, or causing to be made, a false statement to have a false claim paid. Government enforcement agencies and private whistleblowers have initiated investigations or brought private lawsuits against pharmaceutical companies for a variety of allegedly improper promotional or marketing activities, such as allegedly inflating drug prices they report to pricing services, which in turn were used by the government to set Medicare and Medicaid reimbursement rates; allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product; or engaging in promotion for off-label uses. Additionally, the Health Care Reform Laws amended the federal False Claims Act such that a violation of the federal anti-kickback statute can serve as a basis for liability under the False Claims Act;

- HIPAA makes it a crime to knowingly and willfully execute or attempt to execute a scheme to defraud any healthcare benefit program and also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- the federal false statements statute prohibits, among other things, knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;

the Open Payments program requires manufacturers of drugs, devices, biologics and medical supplies reimbursable under Medicare and Medicaid to report to the Department of Health and Human Services information related to payments and other transfers of value to physicians and teaching hospitals, as well as physician ownership and investment interests, and provides for public reporting of the data reported by manufacturers;

the FCPA prohibits U.S. companies and their representatives from paying, offering to pay, promising or authorizing the payment of anything of value to any foreign government official, government staff member, political party or political candidate for the purpose of obtaining or retaining business or to otherwise obtain favorable treatment or influence a person working in an official capacity, and encompasses many healthcare professionals in many countries under the definition of a foreign government official;

the Bribery Act, which applies to U.S. companies such as ourselves that conduct business in the United Kingdom, proscribes giving and receiving bribes in the public and private sectors, bribing a foreign public official and failing to have adequate procedures to prevent employees and other agents from giving bribes; and

analogous state laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers. In addition, some state laws require pharmaceutical companies to comply with the

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pharmaceutical industry s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government. Other states require pharmaceutical manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures, or prohibit certain marketing-related activities including the provision of gifts, meals or other items to certain healthcare providers.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other providers or entities with whom we do business are found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could also harm our financial condition. Responding to government investigations or whistleblower lawsuits, defending any claims raised, and any resulting fines, damages, penalties, settlement payments or administrative actions, as well as any related actions brought by stockholders or other third parties, could have a material impact on our reputation, business and financial condition and divert the attention of our management from operating our business.

***Our corporate compliance efforts cannot guarantee that we are in compliance with all potentially applicable regulations.***

The development, manufacturing, pricing, sales, coverage and reimbursement of our products, together with our general operations, are and will be subject to extensive regulation by federal, state and other authorities within the United States and numerous entities outside of the United States. While we have implemented a corporate compliance program based on what we believe are the current best practices, we cannot provide any assurance that governmental authorities will find that our business practices comply with current or future administrative or judicial interpretations of potentially applicable laws and regulations. If we fail to comply with any of these laws and regulations, we could be subject to a range of regulatory actions, including suspension or termination of clinical trials, the failure to approve a product candidate, restrictions on our products or manufacturing processes, withdrawal of ONIVYDE or other products from the market, significant fines, disqualification or debarment from participation in federally-funded healthcare programs or other sanctions or litigation, any of which events may have a significant adverse impact on our business.

**Risks Related to Data Protection and Cybersecurity**

***Our failure to comply with data protection laws and regulations could lead to government enforcement actions, private litigation and/or adverse publicity and could negatively affect our operating results and business.***

We are subject to data protection laws and regulations that address privacy and data security. The legislative and regulatory landscape for data protection continues to evolve, and in recent years there has been an increasing focus on privacy and data security issues. In the United States, numerous federal and state laws and regulations, including state data breach notification laws, state health information privacy laws and federal and state consumer protection laws govern the collection, use, disclosure and protection of health-related and other personal information. Failure to comply with data protection laws and regulations could result in government enforcement actions, which could include civil or criminal penalties, private litigation and/or adverse publicity and could negatively affect our operating

results and business. In addition, we may obtain health information from third parties (e.g., healthcare providers who prescribe our products) that are subject to privacy and security requirements under HIPAA. We could be subject to criminal penalties if we knowingly obtain or disclose individually identifiable health information in a manner that is not authorized or permitted.

***Significant disruptions of information technology systems or security breaches could adversely affect our business.***

We are increasingly dependent upon information technology systems, infrastructure and data to operate our business. In the ordinary course of business, we collect, store and transmit large amounts of confidential information (including, among other things, trade secrets or other intellectual property, proprietary business information and personal information). It is critical that we do so in a secure manner to maintain the confidentiality and integrity of such confidential information. We also have outsourced elements of our operations to third parties, and as a result we manage a number of third-party vendors who may or could have access to our confidential information. The size and complexity of our information technology systems, and those of third-party vendors with whom we contract, and the large amounts of confidential information stored on those systems, make such systems vulnerable to service interruptions or to security breaches from inadvertent or intentional actions by our employees, third-party vendors, and/or business

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partners, or from cyber-attacks by malicious third parties. Cyber-attacks are increasing in their frequency, sophistication and intensity, and have become increasingly difficult to detect. Cyber-attacks could include the deployment of harmful malware, denial-of-service attacks, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information.

Significant disruptions of our information technology systems or security breaches could adversely affect our business operations and/or result in the loss, misappropriation and/or unauthorized access, use or disclosure of, or the prevention of access to, confidential information, including, among other things, trade secrets or other intellectual property, proprietary business information and personal information, and could result in financial, legal, business and reputational harm to us. For example, any such event that leads to unauthorized access, use or disclosure of personal information, including personal information regarding our patients or employees, could harm our reputation, require us to comply with federal and/or state breach notification laws and foreign law equivalents, and otherwise subject us to liability under laws and regulations that protect the privacy and security of personal information. Security breaches and other inappropriate access can be difficult to detect, and any delay in identifying them may lead to increased harm of the type described above. While we have implemented security measures to protect our information technology systems and infrastructure, there can be no assurance that such measures will prevent service interruptions or security breaches that could adversely affect our business.

**Risks Related to Employee Matters and Managing Growth**

***Our future success depends on our ability to retain our Chief Executive Officer and other key executives and to attract, retain and motivate qualified personnel.***

We are highly dependent on Robert J. Mulroy, our President and Chief Executive Officer, and the other principal members of our executive and scientific teams. Although we have formal employment agreements with each of our executive officers, these agreements do not prevent our executives from terminating their employment with us at any time. We do not maintain key person insurance for any of our executives or other employees. The loss of the services of any of these persons could impede the achievement of our research, development and commercialization objectives.

Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel will also be critical to our success. We may not be able to attract and retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us.

***We have expanded, and expect to continue to expand, our development, manufacturing, regulatory and sales and marketing capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.***

We have grown significantly in the number of our employees and the scope of our operations, particularly in the areas of drug development, manufacturing, regulatory affairs and sales and marketing, and we expect to continue to grow in these areas. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and

train additional qualified personnel. The physical expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

***We have entered into and may continue to enter into or seek to enter into business combinations and acquisitions which may be difficult to integrate, disrupt our business, divert management attention or dilute stockholder value.***

As part of our business strategy, we may enter into business combinations and acquisitions. Although we acquired Hermes in October 2009, we have limited experience in making acquisitions. In addition, acquisitions are typically accompanied by a number of risks, including:

the difficulty of integrating the operations and personnel of the acquired companies;

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- the potential disruption of our ongoing business and distraction of management;
- potential unknown liabilities and expenses;
- the failure to achieve the expected benefits of the combination or acquisition;
- the maintenance of acceptable standards, controls, procedures and policies; and
- the impairment of relationships with employees as a result of any integration of new management and other personnel.

If we are not successful in completing acquisitions that we may pursue in the future, we would be required to reevaluate our business strategy and we may have incurred substantial expenses and devoted significant management time and resources in seeking to complete the acquisitions. In addition, with future acquisitions, we could use substantial portions of our available cash as all or a portion of the purchase price. As we did for the acquisition of Hermes, we could also issue additional securities as consideration for these acquisitions, which could cause our stockholders to suffer significant dilution.

**Risks Related to Our Common Stock**

***Our executive officers, directors and principal stockholders maintain the ability to significantly influence all matters submitted to stockholders for approval.***

Our executive officers, directors and stockholders who own more than 5% of our outstanding common stock, in the aggregate, beneficially own a large portion of our capital stock. As a result, if these stockholders were to choose to act together, they would be able to significantly influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would significantly influence the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of voting power could allow, delay or prevent an acquisition of our company on terms that other stockholders may desire.

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

Provisions in our corporate charter and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which our stockholders might otherwise receive a premium for their shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Because our board of directors is responsible for appointing the members of our management team, these provisions could in turn affect any attempt by our stockholders to replace current members of our management team. Among others, these provisions:

allow the authorized number of our directors to be changed only by resolution of our board of directors;

establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;

require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;

limit who may call stockholder meetings;

authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a poison pill that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and

require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or bylaws.

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Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

Further, the repurchase right under the convertible notes in connection with a fundamental change (as defined therein) and any increase in the conversion rate in connection with a make-whole fundamental change could also discourage a potential acquirer.

***Our stock price has been and may in the future be volatile, which could cause holders of our common stock to incur substantial losses.***

Our stock price has been and in the future may be subject to substantial price volatility. The stock market in general and the market for biotechnology 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, our stockholders could incur substantial losses. The market price for our common stock may be influenced by many factors, including:

- our ability to successfully commercialize ONIVYDE in combination with 5-FU and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy;
- the success of competitive products or technologies;
- results of clinical trials of our product candidates or those of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patents or other proprietary rights;
- the recruitment or departure of key personnel;
- 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 issuance of new or changed securities analysts reports or recommendations;

activism by any single large stockholder or combination of stockholders;

general economic, industry and market conditions; and

the other factors described in this Risk Factors section.

***The indenture governing our 11.5% senior secured notes due 2022 imposes significant operating and financial restrictions on us and our subsidiaries that may prevent us from pursuing certain business opportunities and restrict our ability to operate our business.***

On December 22, 2015, we issued $175.0 million in aggregate principal amount of 11.5% senior secured notes due 2022. The indenture governing the 2022 notes contains covenants that restrict our and our subsidiaries ability to take various actions, including, among other things:

the incurrence of debt;

the issuance of our preferred stock;

the payment of dividends, the repurchase of shares and making certain other restricted payments;

the prepayment, redemption or repurchase of subordinated debt;

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the sale, lease or transfer of property and assets;

engaging in transactions with affiliates; and

the making of investments other than those permitted by the indenture.

The indenture specifies a number of events of default, some of which are subject to applicable grace or cure periods, including, among other things, non-payment defaults, covenant defaults, cross-defaults to other material indebtedness, bankruptcy and insolvency defaults, and non-payment of material judgments.

Our ability to comply with these covenants will likely be affected by many factors, including events beyond our control, and we may not satisfy those requirements. Our failure to comply with our obligations could result in an event of default under our other indebtedness and the acceleration of our other indebtedness, in whole or in part, could result in an event of default under the indenture governing the 2022 notes.

The restrictions contained in the indenture governing the 2022 notes could also limit our ability to plan for or react to market conditions, meet capital needs or otherwise restrict our activities or business plans and adversely affect our ability to finance our operations, enter into acquisitions or to engage in other business activities that would be in our interest.

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

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

***Future sales of shares of our common stock, including by us or our directors and executive officers or shares issued upon the exercise of currently outstanding options and warrants, or upon conversion of our outstanding convertible notes, could cause the market price of our common stock to drop significantly, even if our business is doing well.***

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

**Item 1B. Unresolved Staff Comments**

None.

**Item 2. Properties**

Our principal facilities consist of approximately 167,000 square feet of research, manufacturing and office space located at One Kendall Square in Cambridge, Massachusetts. The lease on our principal facilities expires in June 2019. We retain an option to renew the lease on all of our current space for an additional period of either one or five years.

The facilities of our Silver Creek subsidiary consist of approximately 1,878 square feet of research and office space located in San Francisco, California. The lease on this space expires in December 2016, subject to an option to extend the lease for six additional months.

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**Item 3. Legal Proceedings**

None.

**Item 4. Mine Safety Disclosures**

Not applicable.

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## PART II

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

Our common stock is publicly traded on the NASDAQ Global Market under the symbol MACK . The following table sets forth, for the quarterly periods indicated, the high and low sales prices of our common stock as reported on the NASDAQ Global Market for each quarter in the years ended December 31, 2014 and 2015.

| | High | Low |
|---|---|---|
| **Year ended December 31, 2014** | | |
| First Quarter | $ 6.46 | $ 4.51 |
| Second Quarter | $ 8.25 | $ 4.13 |
| Third Quarter | $ 8.99 | $ 5.53 |
| Fourth Quarter | $ 11.47 | $ 7.36 |
| **Year ended December 31, 2015** | | |
| First Quarter | $ 12.50 | $ 8.37 |
| Second Quarter | $ 13.84 | $ 10.50 |
| Third Quarter | $ 12.59 | $ 7.57 |
| Fourth Quarter | $ 10.85 | $ 7.21 |

**Holders**

As of January 31, 2016, there were approximately 179 holders of record of our common stock. This number does not include beneficial owners whose shares are held by nominees in street name.

**Dividends**

We have never declared or paid cash dividends on our common stock, and we do not expect to pay any cash dividends on our common stock in the foreseeable future. In addition, the terms of our existing debt agreements limit our ability to pay dividends. See Item 7. Management s Discussion and Analysis of Financial Condition and Results of Operations Liquidity and Capital Resources Borrowings for more information regarding our debt agreements.

**Corporate Performance Graph**

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

The following graph compares the performance of our common stock to the NASDAQ Composite Index and to the NASDAQ Biotechnology Index from March 29, 2012 (the first date that shares of our common stock were publicly traded) through December 31, 2015. The comparison assumes $100 was invested after the market closed on March 29, 2012 in our common stock and in each of the foregoing indices, and it assumes reinvestment of dividends, if any. The stock price performance included in this graph is not necessarily indicative of future stock price performance.

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COMPARISON CUMULATIVE TOTAL RETURN

Among the NASDAQ Composite Index, the NASDAQ Biotechnology Index and Merrimack Pharmaceuticals, Inc.

**Recent Sales of Unregistered Securities**

On December 22, 2015, we closed a private placement of $175.0 million aggregate principal amount of 2022 notes and entered into an indenture with U.S. Bank National Association, as trustee and collateral agent, governing the 2022 notes. The 2022 notes were sold directly only to qualified institutional buyers within the meaning of Rule 144A under the Securities Act in reliance upon the exemption from the registration requirements of the Securities Act pursuant to Section 4(a)(2) thereof relative to transactions by an issuer not involving any public offering. No underwriters were involved in the sales of the 2022 notes. All purchasers of the 2022 notes represented to us in connection with their purchase that they were qualified institutional buyers and were acquiring the shares for their own account for investment purposes and not with a view to resale or distribution thereof in contravention of the Securities Act and that they were capable of evaluating the merits and risks of purchasing the 2022 notes and could bear the economic risks of investing in the 2022 notes for an indefinite period of time, including the complete loss of their investment. The purchasers received written disclosures that the 2022 notes had not been registered under the Securities Act and that any resale must be made pursuant to a registration statement or an available exemption from such registration requirements. We received net proceeds from the private placement of approximately $168.5 million, after deducting private placement and offering expenses payable by us.

**Item 6. Selected Financial Data**

You should read the following selected consolidated financial data together with our consolidated financial statements and the related notes appearing at the end of this Annual Report on Form 10-K and the Management s Discussion and Analysis of Financial Condition and Results of Operations section of this Annual Report on Form 10-K. We have derived the consolidated statements of operations data for the years ended December 31, 2015, 2014 and 2013 and the consolidated balance sheet data as of December 31, 2015 and 2014 from our audited consolidated financial statements included in this Annual Report on Form 10-K. We have derived the consolidated statements of operations data for the years ended December 31, 2012 and 2011 and the consolidated balance sheet data as of December 31, 2013, 2012 and 2011 from our audited consolidated financial statements not included in this Annual Report on Form 10-K. Our historical results for any prior period are not necessarily indicative of results to be expected in any future period.

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| (in thousands, except per share amounts) | Years ended December 31, 2015 | 2014 | 2013 | 2012 | 2011 |
|---|---|---|---|---|---|
| **Consolidated statements of operations data** | | | | | |
| Revenues: | | | | | |
| Product revenues, net | $ 4,328 | $ | $ | $ | $ |
| License and collaboration revenues | 84,930 | 102,756 | 47,786 | 48,921 | 34,215 |
| Total revenues | 89,258 | 102,756 | 47,786 | 48,921 | 34,215 |
| Costs and expenses: | | | | | |
| Cost of product revenues | 46 | | | | |
| Research and development expenses | 160,988 | 138,495 | 147,139 | 125,858 | 100,630 |
| Selling, general and administrative expenses | 57,795 | 30,517 | 21,187 | 15,805 | 14,454 |
| Total costs and expenses | 218,829 | 169,012 | 168,326 | 141,663 | 115,084 |
| Loss from operations | (129,571) | (66,256) | (120,540) | (92,742) | (80,869) |
| Other income and expenses: | | | | | |
| Interest income | 99 | 114 | 166 | 184 | 56 |
| Interest expense (1) | (19,232) | (18,230) | (10,938) | (553) | (13) |
| Other income, net | 917 | 813 | 627 | 1,357 | 1,150 |
| Net loss | (147,787) | (83,559) | (130,685) | (91,754) | (79,676) |
| Less net income (loss) attributable to non-controlling interest | 170 | (268) | 240 | (477) | (453) |
| Net loss attributable to Merrimack Pharmaceuticals, Inc. | $ (147,957) | $ (83,291) | $ (130,925) | $ (91,277) | $ (79,223) |
| Net loss per share available to common stockholders basic and diluted (2) | $ (1.33) | $ (0.80) | $ (1.32) | $ (1.28) | $ (7.67) |
| Weighted-average common shares used in computing net loss per share available to common stockholders basic and diluted (3) | 111,356 | 104,410 | 98,919 | 72,831 | 11,343 |

(1) In July 2013, we issued $125.0 million aggregate principal amount of 4.50% convertible notes due 2020 in an underwritten public offering. In November and December 2012, we borrowed an aggregate principal amount of $40.0 million under a loan agreement with Hercules Technology Growth Capital, Inc., or Hercules. These loans with Hercules were repaid in full in December 2015. In December 2015, we issued $175.0 million aggregate principal amount of 11.50% senior secured notes due 2022 through a private placement.

(2) The numerator in the calculation of net loss per share available to common stockholders basic and diluted for the years ended December 31, 2012 and 2011 includes unaccreted dividends on our convertible preferred stock. Upon closing of our initial public offering in April 2012, all outstanding shares of our convertible preferred stock were converted into 66.3 million shares of common stock.

(3) In April 2012, we closed our initial public offering, which resulted in the sale of approximately 15.0 million shares of common stock and the conversion of all shares of outstanding convertible preferred stock into approximately 66.3 million shares of common stock. In July 2013, we closed an underwritten public offering of common stock, which resulted in the sale of approximately 5.8 million shares of common stock. In July 2015, we

entered into an agreement to sell shares of our common stock through an at the market offering program. We concluded sales under this program in September 2015, having sold approximately 3.8 million shares of common stock.

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| | As of December 31, | | | | |
|---|---|---|---|---|---|
| **(in thousands)** | **2015** | **2014** | **2013** | **2012 (1)** | **2011** |
| **Consolidated balance sheet data** | | | | | |
| Cash and cash equivalents | $ 185,606 | $ 35,688 | $ 65,086 | $ 37,714 | $ 50,454 |
| Marketable securities | | 88,340 | 90,116 | 72,238 | |
| Total assets | 234,880 | 158,506 | 192,233 | 148,949 | 85,299 |
| Loans payable (2) | | 39,550 | 39,082 | 39,830 | |
| Capital lease obligations | | | | | 48 |
| Derivative liability | | | | 196 | |
| 4.50% convertible notes (3) | 88,495 | 80,452 | 72,409 | | |
| 11.50% senior secured notes (4) | 169,160 | | | | |
| Deferred revenues | 101,334 | 94,957 | 75,475 | 80,464 | 85,745 |
| Convertible preferred stock warrants | | | | | 1,516 |
| Total liabilities | 418,569 | 260,577 | 235,361 | 155,369 | 106,990 |
| Non-controlling interest | 239 | 69 | 337 | 97 | 574 |
| Convertible preferred stock | | | | | 268,225 |
| Total stockholders deficit | (183,928) | (102,140) | (43,465) | (6,517) | (290,490) |

(1) Upon closing of our initial public offering in April 2012, all outstanding shares of our convertible preferred stock were converted into 66.3 million shares of common stock, all outstanding warrants to purchase shares of convertible preferred stock were converted into warrants to purchase shares of common stock and approximately $4.3 million of cash dividends became payable to the holders of Series B convertible preferred stock.

(2) In November and December 2012, we borrowed an aggregate principal amount of $40.0 million under a loan agreement with Hercules. These loans were repaid in full in December 2015.

(3) In July 2013, we sold an aggregate of 5.8 million shares of our common stock at a price to the public of $5.00 per share and issued $125.0 million aggregate principal amount of convertible notes in concurrent underwritten public offerings, in which we received aggregate net proceeds of approximately $147.3 million, after deducting underwriting discounts and commissions and offering expenses payable by us. $51.9 million net of issuance costs of the aggregate principal amount of the convertible notes is considered a conversion feature and is included as a component of stockholders deficit.

(4) In December 2015, we closed a private placement of $175.0 million aggregate principal amount of 11.50% senior secured notes due 2022 and received net proceeds of approximately $168.5 million, after deducting private placement and offering expenses payable by us.

**Item 7. Management s Discussion and Analysis of Financial Condition and Results of Operations**

*The following discussion of our financial condition and results of operations should be read in conjunction with our financial statements and the notes to those financial statements appearing elsewhere in this Annual Report on Form 10-K. This discussion contains forward-looking statements that involve significant risks and uncertainties. As a result of many factors, such as those set forth in Part I, Item 1A. Risk Factors of this Annual Report on Form 10-K, which are incorporated herein by reference, our actual results may differ materially from those anticipated in these forward-looking statements.*

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**Overview**

We are a biopharmaceutical company discovering, developing and commercializing innovative medicines consisting of novel therapeutics paired with diagnostics for the treatment of cancer. We were founded by a team of scientists from The Massachusetts Institute of Technology and Harvard University who sought to develop a systems biology-based approach to biomedical research. The core of our approach to systems biology is to apply multidisciplinary and multitechnology capabilities to build functional and predictive computational models of biological systems, such as cell signaling networks, that allow us to engineer treatments that are directed at the mechanisms of disease. We view cancer as a complex engineering challenge. Through systems biology, which brings together the fields of biology, computing and engineering, we aim to decrease uncertainty in drug development and clinical validation, and move discovery efforts beyond trial and error. Our mission is to employ these insights to provide patients, physicians and the healthcare system with the medicines, tools and information to deliver integrated healthcare solutions that improve both the quality of outcomes and the efficiency of care.

We have one marketed therapeutic oncology product and multiple targeted therapeutic oncology candidates in clinical development. Our most advanced program is our therapeutic MM-398, which we market in the United States under the brand name ONIVYDE. On October 22, 2015, the U.S. Food and Drug Administration, or FDA, and the Taiwan Food and Drug Administration, or TFDA, approved the use of ONIVYDE in combination with fluorouracil, or 5-FU, and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy in the United States and Taiwan, respectively. In addition, the European Medicines Agency, or EMA, has accepted for review a Marketing Authorization Application, or MAA, filed by our collaboration partner Baxalta for ONIVYDE in combination with 5-FU and leucovorin for the treatment of adult patients with metastatic adenocarcinoma of the pancreas who have been previously treated with gemcitabine-based therapy.

In addition to ONIVYDE and our product candidates in clinical development, we have multiple product candidates in preclinical development and a discovery effort advancing additional candidate medicines. We have tailored ONIVYDE and our other product candidates to target specific disease mechanisms that our research suggests are common across many solid tumor types. We believe that ONIVYDE and our other product candidates have the potential to address major unmet medical needs.

We have devoted substantially all of our resources to our drug discovery and development efforts, including advancing our systems biology approach, conducting clinical trials for our product candidates, protecting our intellectual property, preparing for commercial launch of ONIVYDE and providing general and administrative support for these operations. We began to generate revenue from product sales for the first time in the fourth quarter of 2015 and, to date, have financed our operations primarily through private placements of our convertible preferred stock, collaborations, public offerings of our securities and secured debt financings. Through December 31, 2015, we have received $268.2 million from the sale of convertible preferred stock and warrants, $126.7 million of net proceeds from the sale of common stock during our April 2012 initial public offering and July 2013 follow-on underwritten public offering, $38.6 million of net proceeds from our 2015 at the market offering program, or the ATM offering, $39.6 million of net proceeds from a secured debt financing, $120.6 million of net proceeds from the issuance of 4.50% convertible notes due 2020, or the convertible notes, in our July 2013 underwritten public offering, $168.5 million of net proceeds from the issuance of 11.50% senior secured notes due 2022, or the 2022 notes, and $434.6 million of upfront license fees, milestone payments, reimbursement of research and development costs and manufacturing services and other payments from our collaborations. We have also entered into an arrangement to use our manufacturing capabilities to manufacture drug product on behalf of a third-party pharmaceutical company, for which we have received $3.9 million in upfront fees and reimbursements as of December 31, 2015. As of December 31, 2015, we had unrestricted cash and cash equivalents and marketable securities of $185.6 million.

At our currently planned spending rates, we believe that our existing financial resources, together with anticipated net product revenues and net royalty payments from sales of ONIVYDE and the net milestone payments and reimbursements we expect to receive under our Baxalta collaboration, will be sufficient to fund our operations for at least the next twelve months.

On July 13, 2015, we entered into a sales agreement with Cowen and Company, LLC, or Cowen, to sell, from time to time, shares of our common stock having an aggregate sales price of up to $40.0 million through the ATM offering under which Cowen acted as sales agent. We concluded sales under the ATM offering in September 2015, having sold approximately 3.8 million shares of common stock and generating approximately $38.6 million in net proceeds, after deducting commissions and offering expenses.

On December 22, 2015, we closed a private placement of $175.0 million aggregate principal amount of 11.50% 2022 notes, and entered into an indenture with U.S. Bank National Association as trustee and collateral agent. As a result of the 2022 notes, we received net proceeds of approximately $168.5 million, after deducting private placement and offering expenses payable by us.

We have never been profitable and, as of December 31, 2015, we had an accumulated deficit of $802.2 million. Our net loss was $147.8 million for the year ended December 31, 2015, $83.6 million for the year ended December 31, 2014 and $130.7 million for the year ended December 31, 2013. We expect to continue to incur significant expenses and operating losses for at least the next several years. We expect to continue to incur significant research and development expenses in connection with our ongoing activities,

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particularly as we continue the research, development and clinical trials of our product candidates, including multiple simultaneous clinical trials for certain product candidates, some of which have entered or we expect will be entering late stage clinical development. In addition, in connection with supporting commercial sales of ONIVYDE and with seeking and possibly obtaining regulatory approval of any of our other product candidates, we expect to incur significant commercialization expenses for product sales, marketing, manufacturing and distribution. Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances, licensing arrangements and other marketing and distribution arrangements. We may be unable to raise capital when needed or on attractive terms, which would force us to delay, limit, reduce or terminate our research and development programs or commercialization efforts. We will need to generate significant revenues to achieve profitability, and we may never do so.

**Strategic Partnerships, Licenses and Collaborations**

***Baxalta***

On September 23, 2014, we entered into a license and collaboration agreement with Baxter International Inc., Baxter Healthcare Corporation and Baxter Healthcare SA, which we refer to as the Baxalta agreement, for the development and commercialization of MM-398 outside of the United States and Taiwan, or the licensed territory. In connection with Baxter International Inc. s separation of the Baxalta business, the Baxalta agreement was assigned to Baxalta during the second quarter of 2015. As part of the Baxalta agreement, we granted Baxalta an exclusive, royalty-bearing right and license under our patent rights and know-how to develop and commercialize MM-398 in the licensed territory. Baxalta is responsible for using commercially reasonable efforts to develop, obtain regulatory approvals for and, following regulatory approval, commercializing ONIVYDE in the licensed territory. A joint steering committee comprised of an equal number of representatives from each of Baxalta and us is responsible for approving changes to the global development plan for ONIVYDE, including all budgets, and overseeing the parties development and commercialization activities with respect to ONIVYDE. Unless otherwise agreed, we will be responsible for conducting all clinical trials contemplated by the global development plan for ONIVYDE and manufacturing all clinical material needed for such trials.

Under the terms of the Baxalta agreement, we received a $100.0 million upfront, nonrefundable cash payment in September 2014. In addition, we are eligible to receive from Baxalta (i) up to an aggregate of $100.0 million upon the achievement of specified research and development milestones, of which we have received $62.5 million from Baxalta through December 31, 2015, (ii) up to an aggregate of $520.0 million upon the achievement of specified regulatory milestones, of which we have received $20.0 million from Baxalta as of December 31, 2015, and (iii) up to an aggregate of $250.0 million upon the achievement of specified sales milestones. Under the terms of the Baxalta agreement, we will bear up to the first $98.8 million of costs related to the development of ONIVYDE for pancreatic cancer patients who have not previously received gemcitabine-based therapy; however, we expect most of these costs to be offset by payments received upon the achievement of clinical trial-related milestones. We will share equally with Baxalta all other clinical trial costs contemplated by the global development plan. We are also entitled to tiered, escalating royalties ranging from sub-teen double-digits to low twenties percentages of net sales of MM-398 in the licensed territory.

We expect to enter into a commercial supply agreement with Baxalta pursuant to which we will supply ONIVYDE bulk drug substance to Baxalta and, at Baxalta s option, may manage fill and finish activities to be conducted by a third-party contract manufacturer for Baxalta. Baxalta also has the option to manufacture ONIVYDE itself, in which case we will perform a technology transfer of our manufacturing process to Baxalta.

If not terminated earlier by either party, the Baxalta agreement will expire upon expiration of all royalty and other payment obligations of Baxalta under the Baxalta agreement. Either party may terminate the Baxalta agreement in the event of an uncured material breach by the other party. Baxalta may also terminate the Baxalta agreement on a product-by-product, country-by-country or sub-territory-by-sub-territory basis or in its entirety, for its convenience, upon 180 days prior written notice. In addition, we may terminate the Baxalta agreement if Baxalta challenges or supports any challenge of our licensed patent rights.

Under the Baxalta agreement, Baxalta has also agreed that, subject to limited exceptions, until September 23, 2017, neither Baxalta nor any of its affiliates will (i) effect or seek, offer or propose to effect, or cause or participate in or in any way advise, assist or encourage any other person to effect or seek, offer or propose to effect or cause or participate in, any acquisition of any of our securities or assets, any tender or exchange offer, merger or other business combination involving us, any recapitalization, restructuring, liquidation, dissolution or other extraordinary transaction with respect to us, or any solicitation of proxies or consents to vote any of our voting securities, (ii) form, join or in any way participate in a group with respect to any of our securities, (iii) otherwise act, alone or in concert with others, to seek to control or influence our management, board of directors or policies, (iv) take any action that might force us to make a public announcement regarding any of the foregoing or (v) enter into any agreements, discussions or arrangements with any third party with respect to any of the foregoing.

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At the inception of the collaboration, we identified the following deliverables as part of the Baxalta agreement: (i) license to develop and commercialize MM-398 in Baxalta s territories, (ii) discovery, research, development and manufacturing services required to complete ongoing clinical trials related to MM-398, (iii) discovery, research, development and manufacturing services needed to complete future clinical trials in further indications related to MM-398, (iv) the option to perform a technology transfer of our manufacturing process related to the production of MM-398 to Baxalta and (v) participation on the joint steering committee.

We concluded that none of the deliverables identified at the inception of the collaboration has standalone value from the other undelivered elements. As such, all deliverables represent a single unit of accounting.

We have determined that the collaboration represents a services agreement and, as such, have estimated the level of effort expected to be completed as a result of providing the identified deliverables. We will recognize revenue from the nonrefundable upfront payment, forecasted non-substantive milestone payments and estimated payments related to discovery, research, development and technology transfer services based on proportional performance as effort is completed over the expected services period, which is estimated to be substantially complete by June 30, 2020. We will periodically review and, if necessary, revise the estimated service period related to our collaboration with Baxalta.

Research, development and regulatory milestones that are considered substantive on the basis of the contingent nature of the milestone will be recognized as revenue in full in the period in which the associated milestone is achieved, assuming all other revenue recognition criteria are met. All sales milestones will be accounted for in the same manner as royalties and recorded as revenue upon achievement of the milestone, assuming all other revenue recognition criteria are met.

During the second quarter of 2015, the EMA accepted for review an MAA filed by Baxalta for MM-398. As a result of this acceptance, we recognized $20.0 million of revenue related to a substantive milestone payment owed from Baxalta. In August 2015, we achieved a $15.0 million milestone related to the submission of the protocol for our Phase 2 clinical trial of MM-398 in front-line metastatic pancreatic cancer. This milestone is a non-substantive milestone, and revenue related to the achievement of this milestone will be recognized through the proportional performance revenue recognition model. In October 2015, we achieved an additional $47.5 million milestone related to the enrollment of the first patient in a Phase 2 clinical trial of MM-398 in front-line pancreatic cancer. This milestone is also a non-substantive milestone, and revenue related to the achievement of this milestone will be recognized through the proportional performance revenue recognition model. During the years ended December 31, 2015 and 2014, we recognized revenue based on the following components of the Baxalta agreement:

| (in thousands) | Year Ended December 31, 2015 | Year Ended December 31, 2014 |
|---|---|---|
| Proportional performance revenue recognition model | $ 64,930 | $ 10,460 |
| Substantive milestones | 20,000 | |
| Total | $ 84,930 | $ 10,460 |

As of December 31, 2015 and 2014, we maintained the following assets and liabilities related to the Baxalta agreement:

| (in thousands) | December 31, 2015 | December 31, 2014 |
|---|---|---|
| Accounts receivable, billed | $ 1,336 | $ |
| Accounts receivable, unbilled | 626 | 1,615 |
| Deferred revenue | 97,365 | 91,156 |

Of the $97.4 million of deferred revenue related to the Baxalta agreement as of December 31, 2015, $50.1 million is classified as current in the consolidated balance sheets based upon our estimate of revenue that will be recognized under the proportional performance revenue recognition model as a result of effort expected to be completed within the next twelve months.

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***Sanofi***

In September 2009, we entered into a license and collaboration agreement with Sanofi, which we refer to as the Sanofi agreement, for the development and commercialization of MM-121. In June 2014, we agreed with Sanofi to terminate the Sanofi agreement effective December 17, 2014. In connection with the agreement to terminate the Sanofi agreement, among other things, Sanofi transferred ownership of the investigational new drug application for MM-121 back to us in July 2014, and we waived Sanofi s obligation to reimburse us for MM-121 development costs incurred after the effective termination date. As a result of the termination of the Sanofi agreement, we are not entitled to receive any additional fees, milestone payments or reimbursements from the collaboration.

We received total milestone payments of $25.0 million pursuant to the Sanofi agreement. Under the Sanofi agreement, Sanofi was responsible for all MM-121 development and manufacturing costs. Sanofi reimbursed us for internal time at a designated full-time equivalent rate per year and reimbursed us for direct costs and services related to the development and manufacturing of MM-121.

We recognized cost reimbursements for MM-121 development services within the period they were incurred and billable. Billable expenses were defined during each specified budget period. In the event that total development services expense incurred and expected to be incurred during any particular budget period exceeded the total contractually allowed billable amount for development services during that period, we recognized only a percentage of the development services incurred as revenue during that period.

At the inception of the collaboration, we determined that the license, the right to future technology, back-up compounds, participation on steering committees and manufacturing services performance obligations comprising the Sanofi agreement represented a single unit of accounting. As we could not reasonably estimate our level of effort over the collaboration, we recognized revenue from the upfront payment, milestone payment and manufacturing services payments using the contingency-adjusted performance model over the expected development period, which was initially estimated to be 12 years from the effective date of the Sanofi agreement.

As a result of the agreement to terminate the Sanofi agreement, the development period was revised to end as of December 17, 2014 and the balance of deferred revenue remaining as of April 1, 2014 was recognized prospectively on a straight-line basis over the remaining development period, ending on December 17, 2014.

We recognized no revenue under the Sanofi agreement during the year ended December 31, 2015. During the years ended December 31, 2014 and 2013, we recognized revenue based on the following components of the Sanofi agreement:

| | Years ended December 31, | |
|---|---|---|
| **(in thousands)** | **2014** | **2013** |
| Upfront payment | $ 39,306 | $ 5,000 |
| Milestone payment | 16,377 | 2,083 |
| Development services | 18,904 | 36,283 |
| Manufacturing services and other | 17,709 | 3,867 |
| Total | $ 92,296 | $ 47,233 |

We performed development services for which revenue was recognized under the Sanofi agreement in accordance with the specified budget period. During the year and specified budget periods ended December 31, 2013, we

performed $10.1 million of development services in excess of recognized revenue. Of this amount, approximately $5.8 million was recognized as increased revenue in the year ended December 31, 2014 related to expenses incurred prior to December 31, 2013 upon receiving budget approval for these overruns.

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As of December 31, 2015, we maintained no assets or liabilities related to the Sanofi agreement. As of December 31, 2014, we maintained the following assets and liabilities related to the Sanofi agreement:

| (in thousands) | December 31, 2014 |
|---|---|
| Accounts receivable, billed | $ 369 |
| Accounts receivable, unbilled | 1,282 |
| Deferred revenues | |

***Actavis***

In November 2013, we entered into a development, license and supply agreement with Watson Laboratories, Inc., or Actavis, which we refer to as the Actavis agreement, pursuant to which we will develop, manufacture and exclusively supply the bulk form of doxorubicin HCl liposome injection, or the initial product, to Actavis. The Actavis agreement was subsequently amended in January 2015 to transfer certain responsibilities from us to Actavis in exchange for reducing the aggregate milestone payments that we are eligible to receive by $0.4 million. Under the Actavis agreement, Actavis is responsible for all costs related to finished product processing and global commercialization. Pursuant to the Actavis agreement, we have also agreed to develop additional products for Actavis in the future, the identities of which will be mutually agreed upon. We are eligible to receive up to $15.1 million, of which $3.9 million has been received through December 31, 2015, and the remainder is expected to be received in development funding and development, regulatory and commercial milestone payments related to the initial product. We will also receive a double digit percentage of net profits on global sales of the initial product and any additional products. We will manufacture and supply the initial product to Actavis in bulk form at an agreed upon unit price.

The Actavis agreement will expire with respect to the initial product and any additional products developed in the future ten years after Actavis first sale of the applicable product, unless terminated earlier, and will automatically renew for additional two year periods thereafter unless either party provides notice of non-renewal. Either party may terminate the Actavis agreement in the event of an uncured material breach or bankruptcy filing by the other party. Actavis may also terminate the agreement for convenience in specified circumstances upon 90 days prior written notice.

We applied revenue recognition guidance to determine whether the performance obligations under this collaboration, including the license, participation on steering committees, development services, and manufacturing and supply services, could be accounted for separately or as a single unit of accounting. We determined that these obligations represent a single unit of accounting and will recognize revenue as product is supplied to Actavis. Therefore, we have recorded $4.0 million and $3.8 million of total billed and billable milestones and development expenses related to the Actavis agreement as deferred revenue as of December 31, 2015 and December 31, 2014, respectively. We expect to recognize this revenue over the ten year period that begins after Actavis first sale of applicable product under the Actavis agreement.

***Silver Creek Pharmaceuticals, Inc.***

In 2010, we established Silver Creek Pharmaceuticals, Inc., or Silver Creek, as a subsidiary. Silver Creek s mission is to apply our systems biology approach to the research and development of regenerative medicines to repair the heart. On December 31, 2014 and December 31, 2013, $1.0 million and $2.6 million, respectively, of convertible notes and related accrued interest converted to shares of Series A preferred stock of Silver Creek. During the year ended December 31, 2015, Silver Creek issued and sold a total of 1.6 million shares of its Series B preferred stock at a price

per share of $1.35 to investors and received net proceeds of $2.1 million, after deducting issuance costs. As of December 31, 2015 and 2014, we owned approximately 56% and 60%, respectively, of the outstanding preferred stock of Silver Creek. We concluded that Silver Creek is a variable interest entity and that we are the primary beneficiary. We have the ability to direct the activities of Silver Creek through our ownership percentage and through the board of directors seats controlled by us and our de facto agents, and therefore, we consolidate Silver Creek for financial reporting purposes.

In the future, we may consider forming additional businesses or business units to apply our systems biology approach to multiple additional disease areas outside the oncology field. We expect to do so in some cases, as with Silver Creek, through the establishment of separately funded companies.

**Financial Obligations Related to the License and Development of MM-398**

In September 2005, Hermes BioSciences, Inc., or Hermes, which we acquired in October 2009, entered into a license agreement with PharmaEngine under which PharmaEngine received an exclusive license to research, develop, manufacture and commercialize MM-398 in Europe and certain countries in Asia. In May 2011, we entered into a new agreement with PharmaEngine under which we reacquired all previously licensed rights for MM-398, other than rights to commercialize MM-398 in Taiwan. As a

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result, we had the exclusive right to commercialize MM-398 in all territories in the world, except for Taiwan, where PharmaEngine has an exclusive commercialization right. Upon entering into the May 2011 agreement with PharmaEngine, we paid PharmaEngine a $10.0 million upfront license fee. In addition, we made a milestone payment of $5.0 million to PharmaEngine in connection with dosing the first patient in our Phase 3 clinical trial of MM-398, which occurred and was paid in the first quarter of 2012.

On September 22, 2014, we amended the PharmaEngine agreement to redefine sublicense revenue and reduce the portion of sublicense revenue that we are required to pay to PharmaEngine. As a result of this amendment, we made a $7.0 million milestone payment to PharmaEngine. Additionally, as a result of this amendment, a previously contingent $5.0 million milestone payment was paid in the second quarter of 2015. Prior to the amendment of the PharmaEngine agreement, this milestone payment was contingent upon the award of certain specified regulatory designations. These milestone payments were recognized as research and development expense during the year ended December 31, 2014.

Since entering into the PharmaEngine agreement, we have paid PharmaEngine an aggregate of $38.0 million in upfront license fees and milestone payments, including an $11.0 million milestone payment made in July 2015 in connection with the EMA s acceptance for review of an MAA for MM-398, which occurred, and was recognized as research and development expense, in the second quarter of 2015. In addition to these amounts, we could also be required to pay PharmaEngine up to an additional $60.0 million in aggregate regulatory milestones, $38.5 million in sublicense fees and $130.0 million in aggregate sales milestones, in each case with respect to Europe and certain countries in Asia. PharmaEngine is also entitled to tiered royalties on net sales of MM-398 in Europe and certain countries in Asia. The royalty rates under the PharmaEngine agreement range from high single digits up to the low teens as a percentage of our net sales of MM-398 in these territories. Under the PharmaEngine agreement, we are responsible for all future development costs of MM-398 except those required specifically for regulatory approval in Taiwan. During the years ended December 31, 2015, 2014 and 2013, we recognized research and development expenses of $11.4 million, $12.6 million and $1.5 million, respectively, related to the PharmaEngine agreement, which included $11.0 million of expenses related to milestone payments in 2015 and $12.0 million of expenses related to milestone payments in 2014. Our financial obligations under other license and development agreement are summarized below under Liquidity and Capital Resources Contractual obligations and commitments.

**Financial Operations Overview**

***Revenues***

The majority of our revenue to date has been derived from license fees, milestone payments and research, development, manufacturing and other payments received from collaborations, and, to a lesser extent, from grant payments received from the National Cancer Institute as well sales of ONIVYDE. In the future, we may generate revenue from a combination of product sales, license fees, milestone payments and research, development and manufacturing payments from collaborations and royalties from the sales of products developed under licenses of our intellectual property.

Upon the FDA s approval of ONIVYDE in the fourth quarter of 2015, we began commercially selling ONIVYDE within the United States. For the year ended December 31, 2015, we recognized net product revenues of $4.3 million. As described in further detail below, we estimate our net product revenues by deducting from our gross product revenues trade allowances, estimated rebates and chargeback discounts, estimated reserves for product returns and estimated costs of other incentives offered to patients. We expect such net product revenues to increase in 2016 as compared to 2015 as ONIVYDE continues to gain market penetration.

License and collaboration revenues in 2015 under the Baxalta agreement increased as compared to 2014, as we have performed a full year of services under the Baxalta agreement. As a result, we recognized additional revenue under our proportional performance revenue recognition model. An additional increase in 2015 revenue occurred as a result of achieving a $20.0 million substantive regulatory milestone in the second quarter of 2015 related to the EMA s acceptance for review of an MAA for MM-398. There was not a one-time increase in revenue related to either the $15.0 million research and development milestone or the $47.5 million research and development milestone that were achieved under the Baxalta agreement in the third and fourth quarters of 2015, respectively. These milestones were considered non-substantive milestones and as such were included as part of our proportional performance revenue recognition model and revenue related to them will be recognized as effort is completed over the expected services period of the Baxalta collaboration. We expect that revenues recognized in 2016 under the Baxalta agreement will exceed revenues recognized in 2015, as we expect to achieve additional substantive regulatory milestones in 2016 that will result in one time increases to license and collaboration revenues.

We did not recognize any revenue related to the Sanofi agreement during the year ended December 31, 2015, nor do we anticipate recording any revenues related to the Sanofi agreement in the future, due to the termination of the Sanofi agreement effective December 17, 2014.

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***Cost of product revenues***

Cost of product revenues consists of manufacturing costs of product sold, including shipping and handling costs, as well as costs associated with inventory reserves or write-downs. We began to capitalize costs associated with the production of ONIVYDE upon receipt of FDA approval on October 22, 2015. Costs incurred prior to receipt of marketing approval of ONIVYDE were expensed as research and development expense.

As we expensed manufacturing costs related to ONIVYDE prior to receiving FDA approval, we expect that our cost of product revenues as a percentage of net product revenues will increase in future periods as product manufactured prior to FDA approval is consumed. This cost benefit will vary in future periods based on when the components of the specific ONIVYDE lots sold were produced and this benefit is expected to continue to some extent for at least the next twelve months; however, the time period over which this reduced-cost inventory is consumed will depend on a number of factors, including the amount of future ONIVYDE sales, the ultimate use of this inventory in either commercial sales, clinical development or other research activities, and the ability to utilize inventory prior to its expiration date. Additionally, we also expect that costs of revenues as a percentage of net product revenues will increase in the future as we begin to supply ONIVYDE to Baxalta and PharmaEngine to support their sales outside of the United States.

***Research and development expenses***

Research and development expenses consist of the costs associated with our research and discovery activities, including investment in our systems biology approach, conduct of preclinical studies and clinical trials, manufacturing development efforts and activities related to regulatory filings. Our research and development expenses consist of:

- employee salaries and related expenses, which include stock-based compensation and benefits for the personnel involved in our drug discovery and development activities;
- external research and development expenses incurred under agreements with third-party contract research organizations and investigative sites;
- manufacturing material expense for in-house manufacturing and third-party manufacturing organizations and consultants, including costs associated with manufacturing product prior to product approval;
- license fees for and milestone payments related to in-licensed products and technologies; and
- facilities, depreciation and other allocated expenses, which include direct and allocated expenses for rent and maintenance of facilities, depreciation of leasehold improvements and equipment, and laboratory and other supplies.

We expense research and development costs as incurred. Conducting a significant amount of research and development is central to our business model. Product candidates in late stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of late stage clinical trials. We expect to maintain or increase our research and development expenses for the

foreseeable future as we continue to develop our clinical stage product candidates and further advance our preclinical products and earlier stage research and development projects. However, we do not plan to invest in additional development of MM-111 at this time. Such future research and development expenses will include additional regulatory milestone payments that we are required to make under the PharmaEngine agreement.

We use our employee and infrastructure resources across multiple research and development programs. We track expenses related to our most advanced product candidates on a per project basis. Accordingly, we allocate internal employee-related and infrastructure costs, as well as third-party costs, to each of these programs. We do not allocate to particular development programs either stock-based compensation expense or expenses related to preclinical programs. Costs that are not directly attributable to specific clinical programs, such as wages related to shared laboratory services, travel and employee training and development, are not allocated and are considered general research and discovery expenses.

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The following table summarizes our principal product development programs, including the research and development expenses allocated to each clinical product candidate, for the years ended December 31, 2015, 2014 and 2013:

| | Years ended December 31, | | |
|---|---|---|---|
| **(in thousands)** | **2015** | **2014** | **2013** |
| MM-398 | | | |