MIRAGEN THERAPEUTICS, INC.
Form 10-K
March 24, 2017

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2016

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: 001-36483

MIRAGEN THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**47-1187261**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification Number)**

6200 Lookout Road, Boulder, CO 80301
(Address of principal executive offices) (Zip Code)

Registrant's telephone number, including area code: (303) 531-5952

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	**The NASDAQ Capital Market**

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

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

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

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, 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). 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.

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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 definitions of “large accelerated filer”, “accelerated filer” and “smaller reporting company” in Rule 12b-2 of the Exchange Act.

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

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

The aggregate market value of the voting stock held by non-affiliates of the registrant, based upon the closing sale price of the Common Stock on June 30, 2016 as reported on The NASDAQ Capital Market, was $3.4 million. Shares of Common Stock held by each executive officer and director and by each person who owns 10% or more of the outstanding Common Stock have been excluded in that such persons may be deemed to be affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

As of March 17, 2017, there were 21,370,063 shares of the registrant's Common Stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

None.

MIRAGEN THERAPEUTICS, INC.

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FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, or this Annual Report, contains forward-looking statements that involve substantial risks and uncertainties for purposes of the safe harbor provided by the Private Securities Litigation Reform Act of 1995. All statements contained in this Annual Report other than statements of historical fact, including statements regarding our strategy, future operations, future financial position, future revenue, projected expenses, prospects, plans and objectives of management are forward-looking statements. The words “believe,” “may,” “will,” “estimate,” “continue,” “anticipate,” “intend,” “plan,” “expect,” “predict,” “potential,” “opportunity,” “goals,” or “should,” and expressions are intended to identify forward-looking statements.

Such statements are based on management’s current expectations and involve risks and uncertainties. Actual results and performance could differ materially from those projected in the forward-looking statements as a result of many factors, including, without limitation:

- We have incurred losses since our inception, have a limited operating history on which to assess our business, and anticipate that we will continue to incur significant losses for the foreseeable future.
- We have never generated any revenue from product sales and may never be profitable.
- Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights.
- Clinical trials are costly, time consuming and inherently risky, and we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities.
- The approach we are taking to discover and develop novel therapeutics using microRNA is unproven and may never lead to marketable products.
- Our microRNA therapeutic product candidates are based on a relatively novel technology, which makes it difficult to predict the time and cost of development and of subsequently obtaining regulatory approval, if at all. To date, no microRNA therapeutics have been approved for marketing in the United States.
- We may not be able to develop or identify technology that can effectively deliver MRG-106, MRG-201 or any other of our microRNA-targeted product candidates to the intended diseased cells or tissues, and any failure in such delivery technology could adversely affect and delay the development of MRG-106, MRG-201 and our other product candidates.
- Our product candidates may cause undesirable side effects or have other properties that could delay or prevent the regulatory approval, limit the commercial viability of an approved label, or result in significant negative consequences following marketing approval, if any.

We have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our financial condition, results of operations, business strategy, short-term and long-term business operations and objectives, and financial needs. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including those described in Part I, Item 1A, "Risk Factors" in this Annual Report. Moreover, we operate in a very competitive and rapidly changing environment. New risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. In light of these risks,

uncertainties and assumptions, the future events and trends discussed in this Annual Report may not occur and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements.

We undertake no obligation to revise or publicly release the results of any revision to these forward-looking statements, except as required by law. Given these risks and uncertainties, readers are cautioned not to place undue reliance on such forward-looking statements. All forward-looking statements are qualified in their entirety by this cautionary statement.

PART I

Item 1. Business

Merger of Signal Genetics, Inc. and Miragen Therapeutics, Inc.

On February 13, 2017 Signal Genetics, Inc., or Signal, and privately-held Miragen Therapeutics, Inc., or Private Miragen, completed the merger and reorganization, or the Merger, in accordance with the terms of the Agreement and Plan of Merger and Reorganization, dated October 31, 2016, or the Merger Agreement, whereby Signal merged with and into Private Miragen, with Private Miragen surviving as a wholly owned subsidiary of Signal. Immediately following the Merger, Signal changed its name to “Miragen Therapeutics, Inc.,” the post-Merger company is referred to in this Annual Report as Miragen. In connection with the closing of the Merger, our common stock began trading on The NASDAQ Capital Market under the ticker symbol “MGEN” on February 14, 2017. Additionally, on February 13, 2017, in connection with the Merger, we completed the sale of all of our intellectual property assets relating to our MyPRS test, or collectively, the MyPRS Assets, a microarray-based gene expression profile assay, pursuant to an Intellectual Property Purchase Agreement, or the IP Purchase Agreement, with Quest Diagnostics Investments LLC, or Quest, dated November 29, 2016. As consideration for the sale of the MyPRS Assets, Quest paid us $0.8 million, plus an additional $0.1 million, as consideration for exercising its right to require us to operate our lab beyond December 31, 2016 and an additional $21,000 for reimbursement of certain amounts paid by us to the University of Texas M.D. Anderson Cancer Center.

Prior to the Merger, Signal was founded in New York as a Delaware limited liability company in January 2010 under the name Myeloma Health LLC. Signal Genetics LLC was formed as a Delaware limited liability company in December 2010. Effective January 1, 2011, substantially all of the member interests in Myeloma Health LLC were exchanged for member interests in Signal Genetics LLC and Myeloma Health LLC became a subsidiary of Signal Genetics LLC. Immediately prior to the pricing of our initial public offering, on June 17, 2014, Signal Genetics LLC converted from a Delaware limited liability company to a Delaware corporation, or the Corporate Conversion. In connection with the Corporate Conversion, each unit of Signal Genetics LLC was converted into a share of common stock of Signal, the members of Signal Genetics LLC became stockholders of Signal and Signal succeeded to the business of Signal Genetics LLC and its consolidated subsidiaries. As used in this report, the words “we,” “us,” “our,” the “Company,” and “Miragen” refer to Miragen Therapeutics, Inc.

Overview

Prior to the Merger, we were a commercial-stage, molecular genetic diagnostic company historically focused on providing innovative diagnostic services that helped physicians make better-informed decisions concerning the care of their patients suffering from cancer.

After the Merger, we are a clinical-stage biopharmaceutical company discovering and developing proprietary RNA-targeted therapeutics with a specific focus on microRNAs and their role in diseases where there is a high unmet medical need. microRNAs are short RNA molecules, or oligonucleotides, that regulate gene expression or activity and play a vital role in influencing the pathways responsible for many disease processes. We believe our experience in microRNA biology and chemistry, drug discovery, bioinformatics, and translational medicine provide it with a potential competitive advantage to identify and develop microRNA-targeted drugs designed to regulate gene pathways to result in disease modification. We use our expertise in systems biology and oligonucleotide chemistry to discover and develop a pipeline of product candidates. Our two lead product candidates, MRG-106 and MRG-201, are currently in Phase 1 clinical trials. Our clinical product candidate for the treatment of certain cancers, MRG-106, is an inhibitor of microRNA-155, or miR-155, which is found at abnormally high levels in several blood cancers. Our clinical product candidate for the treatment of pathological fibrosis, MRG-201, is a replacement for miR-29, which is found at abnormally low levels in a number of pathological fibrotic conditions, including cardiac, renal, hepatic, and pulmonary fibrosis, as well as systemic sclerosis. In addition to our clinical programs, we continue to discover and develop a pipeline of pre-clinical product candidates. The goal of our translational medicine strategy is to progress rapidly to first in human studies once it has established the pharmacokinetics (the movement of drug into, through, and out of the body), pharmacodynamics (the effect and mechanism of action of a drug), safety and manufacturability of the product candidate in preclinical studies.

In February 2016, we administered MRG-106 to the first patient in a multi-site, open-label, dose-ranging Phase 1 clinical trial that seeks to enroll up to 50 patients with a confirmed diagnosis of mycosis fungoides, or MF, which is a subtype of cutaneous T-cell lymphoma, or CTCL, in which malignant T-cells move to the skin and form patches (palpable flat lesions) or plaques and tumors. MRG-106 has been generally safe and well tolerated in the six patients who received the product candidate in Part A, with no significant injection site reactions or dose limiting toxicities. In addition, molecular analyses of patient tissue samples demonstrated changes in gene expression in the tumors consistent with what we believe is the expected mechanism of action of MRG-106 in CTCL lesions. We believe that

these data demonstrate the potential of MRG-106 to regulate appropriate gene pathways to provide clinical benefit in MF patients. Part B of the clinical trial is currently ongoing. As of March 13, 2017, a total of nine patients had completed at least one cycle of dosing in Part B of the clinical trial. One of the nine patients had the drug withheld after the third of six doses but otherwise completed the cycle, including an end of study visit. As of March 13, 2017, MRG-106 had been generally safe and well tolerated in eight of the nine patients who have received the product candidate in Part B. As of March 13, 2017, an additional three patients had started their first cycle of dosing with 300 mg of MRG-106 administered intravenously.

In November 2015, we initiated a single-center Phase 1, double-blind, placebo-controlled, single and multiple dose-escalation clinical trial of MRG-201 enrolling up to 70 healthy volunteers. As of March 13, 2017, 54 volunteers had enrolled in the trial, 47 of whom had received MRG-201. MRG-201 has been generally safe and well tolerated in all volunteers, with no significant injection site reactions. Biomarker analysis demonstrated on-target molecular activity for MRG-201 in human skin, with an apparent dose-dependent effect after a single dose. Preliminary histological analysis indicates that incisions treated with multiple administrations of MRG-201 showed a decrease in formation of fibrous tissue, or fibroplasia, with no apparent detrimental effect on wound healing. We believe these data suggest that MRG-201 may be able to reduce pathological fibrosis and scar formation in human skin.

In addition to MRG-106 and MRG-201, we have a pipeline of wholly-owned, pre-clinical product candidates that target individual microRNAs thought to be at abnormally high or low levels in particular diseases. We believe our experience in microRNA biology and chemistry, drug discovery, bioinformatics, and translational medicine allows us to identify and develop RNA-targeted drugs that are designed to regulate gene pathways to return diseased cells to a healthy state. We believe that our drug discovery and development strategy will enable us to progress our product candidates from pre-clinical discovery to confirmation of mechanism of action in humans quickly and efficiently. The elements of this strategy include identification of biomarkers that may predict clinical benefit and monitoring outcomes in early-stage clinical trials to help guide later clinical development.

The following table illustrates our most advanced programs:

Product Candidate	**Target**	Disease Area	Development Status
Clinical			
MRG-106	miR-155	Blood Cancers	Phase 1 clinical trial
MRG-201	miR-29	Pathological Fibrosis	Phase 1 clinical trial
Pre-Clinical			
MRG-107	miR-155	Neuro-Inflammation	IND Enabling
MRG-110	miR-92	Revascularization	IND Enabling

Our Strategy

We seek to use our expertise and understanding of microRNA biology, oligonucleotide chemistry and product development to create novel products that have the potential to transform the treatment of patients with serious diseases. The key components of our strategy are as follows:

- **Continue to develop MRG-106 in blood cancers.** Our ongoing Phase 1 clinical trial of MRG-106 for the treatment of patients with MF is designed to deliver the necessary data, including mechanistic proof-of-concept as well as appropriate doses and dose schedule to support further development of miR-155 inhibitor, MRG-106, in multiple cancer indications in which elevated levels of miR-155 has been observed. We plan to expand our clinical program to explore the broader utility of MRG-106 in patients with other blood cancers, such as diffuse large B cell lymphoma, leukemia, and virally induced lymphomas. We also intend to initiate a Phase 2 clinical trial of MRG-106 in CTCL using a dose, schedule and route of administration selected based on results obtained in the Phase 1 clinical trial.

- **Continue to develop MRG-201 in pathological fibrosis.** Our ongoing Phase 1 clinical trial of MRG-201 in healthy volunteers, in addition to being a safety and tolerability trial, is designed to serve as a human mechanistic proof-of-concept assessment that helps reduce the risk associated with further development of the product candidate for other forms of pathological fibrosis such as pulmonary, retinal, hepatic and renal fibrosis. This clinical trial is designed to serve as a prelude to a Phase 2 clinical trial in skin or other tissue manifestations of pathological fibrosis. We may pursue additional development of MRG-201 independently or through a strategic alliance.

- **Utilize rare disease development pathways at the FDA and comparable foreign regulatory agencies, where appropriate, to accelerate progression to late stage development and early approval.** For wholly-owned programs, we intend to focus on rare and genetic diseases where RNA modulation may produce clinical benefit so that we can take advantage of regulatory programs intended to expedite drug development. We plan to apply for the regulatory programs for orphan drug designation, fast track, breakthrough therapy designation, and/or priority review when available to potentially reduce clinical trial expense and increase speed to commercialization.

- **Collaborate with other biotechnology and pharmaceutical companies to develop additional product candidates.** We intend to seek out collaborations for additional microRNA targets and development of compounds in our pipeline that require larger clinical trials or extensive commercial infrastructure. For example, we have a multi-target strategic collaboration with Les Laboratoires Servier and the Institut de Recherches Servier, or Servier,

to develop product candidates for the treatment of cardiovascular diseases.

- **Use in-house research and translational expertise to further develop our product candidate pipeline.** Our in-house research team investigates novel microRNA targets identified through internal efforts and academic collaborations. We then seek to establish evidence that the microRNA is implicated in certain diseases. We believe that this internal research and expertise could provide a foundation to develop product candidates for the treatment of a variety of diseases in which microRNA is implicated.

- **Selectively build focused commercial capabilities and establish commercial collaborations to maximize the value of our pipeline.** To date, we have retained all U.S. and Japanese rights to our product candidates in the strategic collaboration with Servier and global rights in all other programs. While we have not yet defined our sales, marketing or product distribution strategy for MRG-106, MRG-201 or any of our other product candidates, our commercial strategy may include the use of strategic alliances, distributors, a contract sales force, or the establishment of our own commercial and specialty sales force to maximize the value of our pipeline.

Our Product Candidates

MRG-106

MRG-106 is an inhibitor of miR-155. We are conducting a Phase 1 clinical trial of MRG-106 in patients with MF. Data reported in scientific literature identifies miR-155 as a cancer-causing microRNA, or oncomiR, with a central role in the development of multiple blood cancers. miR-155 controls a number of validated cancer-related disease targets, including Bruton's Tyrosine Kinase and nuclear factor kappa-light-chain-enhancer of activated B cells. In certain B-cell lymphomas, improvement of clinical outcomes has been associated with normalization of miR-155 levels, and poor prognosis, resistance to treatment and recurrence of the disease are associated with elevated levels of miR-155. In addition to playing a role in B-cell malignancies, miR-155 is elevated in another group of malignant white blood cells, called T-cells, found in skin lesions of patients with MF. We screened a library of locked nucleic acid modified oligonucleotides, and identified MRG-106 as having what we believed was the best potential efficacy and drug-like properties including improved pharmacodynamics in human T- and B-cell lymphoma cell lines.

Mycosis Fungoides

MF is the most common form of a type of blood cancer called CTCL. CTCL occurs when certain types of T-cells become cancerous. These malignant T-cells then form specific types of skin lesions. Although the skin is involved, the skin cells themselves are not cancerous. According to the National Institutes of Health, or NIH, MF usually occurs in adults over age 50, although the disease may occur at any age including in children.

We believe the total population of patients with cutaneous lymphoma in the United States and Canada is approximately 30,000. In a 2012 publication, the Lymphoma Research Foundation estimated the prevalence of MF to be 16,000-20,000 cases in the United States. According to the Leukemia and Lymphoma Society in a 2014 publication, approximately 70% to 80% of patients are diagnosed with early stage MF that impacts only the skin. In these patients, the disease typically has a slow progression, but is accompanied by serious quality of life detriments such as severe itchiness, pain and disfiguration. The five-year survival rate for newly diagnosed patients with CTCL is approximately 90%. In later stage MF and in some early stage patients whose disease progresses, the cancer may involve the lymph nodes, blood and internal organs. The five-year survival rate in later stage patients with CTCL (stages IIB, III, IV) is approximately 20-60% depending on stage.

There are currently no curative therapies for CTCL, and concurrent and consecutive treatments, many with significant adverse effects, tend to be given until loss of response. There is a need for new and improved therapies in CTCL to treat the disease and eliminate symptoms such as itchiness and painful skin lesions and to prolong survival in patients with aggressive disease. Most drugs for CTCL have response rates between 30% and 40%, and response durations tend to be less than a year.

There is no universally accepted standard of care for treatment of MF. Treatment is dependent on stage of disease and responsiveness to previous therapy and is divided into skin-directed therapy and whole body treatments. For certain patients with advanced disease, allogeneic stem cell transplantation may offer prolonged survival, but the five-year survival is only around 50%.

In addition to MF, elevation of miR-155 has been associated with several other blood cancers and certain solid tumors. We believe there is a potential opportunity to develop a companion diagnostic that could detect and quantify levels of miR-155 in circulating blood or malignant cells. We believe this approach may then allow for the selection of patients with elevated miR-155 levels who may be more likely to benefit from MRG-106 treatment and allow the drug to be used selectively in multiple cancers. There are several types of cancer in which high levels of miR-155 have been discovered, including subsets of diffuse large B-cell lymphoma, acute myeloid leukemia, certain virally induced lymphomas such as HTLV-1 associated lymphoma and Burkitt's Lymphoma, Down Syndrome-associated acute lymphocytic leukemia, and other types of cancer. We plan to evaluate additional types of lymphoma and leukemia in Phase 1 clinical trials and intend to explore other potential applications for MRG-106 through additional clinical studies in other tumor types.

MRG-106 Phase 1 Clinical Trial

Trial Design

We are conducting a multi-site, open-label, dose-ranging Phase 1 clinical trial of MRG-106 for the treatment of MF at 11 U.S.-based clinical sites. This clinical trial consists of two parts and is expected to enroll up to 50 patients with MF. Patients may be allowed to be on other medications or background therapies so long as they have had no change in treatment regimen for CTCL, including drug and dose, for more than four weeks prior to enrollment and, in the opinion of the investigator, the patient is currently clinically stable and is likely to remain clinically stable for a minimum of three months after screening.

The primary objectives of this clinical trial are safety and tolerability. Secondary objectives include pharmacokinetic assessments, including measurement of absorption and clearance of MRG-106 from the blood. Additionally, there are several exploratory measures to assess any changes in lesion severity before and after treatment as well as pharmacodynamic and histology assessments. The clinical trial utilizes two validated measures of lesion severity: (i) Composite Assessment of Index Lesion Severity Score, or CAILS, which is a composite measure that assesses the severity of one or more lesions on a patient and (ii) modified Severity Weighted Assessment Tool, or mSWAT, which is an assessment tool that is used to analyze the disease severity over a patient's entire body.

Part A of the clinical trial tested the effect of direct injections of 75 mg of MRG-106 intratumorally. Part A of the clinical trial enrolled six patients, five of whom completed dosing. One patient discontinued the trial due to baseline disease that exceeded trial entry criteria, which was discovered during the first week of the trial and the decision was made to withdraw the patient. In four patients, saline placebo was injected into a separate skin lesion at the same time. After eight to 14 days of treatment, in five patients, injections sites were biopsied and analyzed for drug concentration, molecular evidence of drug activity on target gene expression, and histological evidence of alterations in malignant cell numbers and other immune cell populations. Additionally, as an exploratory endpoint, CAILS scoring was used to assess clinical response.

Part B of the clinical trial is enrolling patients and is designed to assess whole body administration of MRG-106. The first group, or cohort, of patients in Part B started receiving doses of MRG-106 in August 2016 as a subcutaneous injection of 300 mg/dose for four weeks. The next cohorts of three patients each received subcutaneous injections of 600 mg or 900 mg of MRG-106. As of March 13, 2017, three patients had started their first cycle of intravenous dosing with 300 mg of MRG-106. Three patients have received MRG-106 in the extension protocol, two of whom were still receiving MRG-106 in the extension protocol as of March 13, 2017. Additional patients will also be dosed intravenously. Dose escalation is planned to occur adaptively in increments from 100 mg to 300 mg, depending on the safety results observed at each dose level tested. In addition, some patients may receive the drug by a combination of routes, including subcutaneous, intravenous or intratumoral injection. Additional patients may be enrolled at any dose level based on safety and tolerability; however, no more than three patients who are within 28 days of their first dose may be in the study at one time. In addition to safety, tolerability and pharmacokinetics, exploratory pharmacodynamic endpoint assessments and clinical scoring using CAILS and mSWAT is being performed.

Safety, Pharmacokinetics and Pharmacodynamics

As of March 13, 2017, 18 MF patients had received at least one dose of MRG-106. MRG-106 was generally safe and well tolerated at all dose levels tested, with no significant injection site reactions. One patient did not receive all the scheduled treatments due to baseline disease that exceeded trial entry criteria as noted above. A second patient discontinued dosing due to worsening of their skin lesions associated with increased itching, which resolved in response to treatment with prednisone. No drug-related serious adverse events have been reported to date.

Six patients in Part A were administered MRG-106 intratumorally, with up to five 75 mg doses of MRG-106 administered to the same tumor over a period of up to two weeks. Four of these patients were simultaneously treated in a second lesion with a saline placebo solution. All patients who received MRG-106 generally tolerated the administrations well with only minimal redness of the skin at the site of injection noted in one patient. One patient was discontinued from the trial after receiving three doses of MRG-106 due to rapid progression of disease, which began shortly before the initiation of dosing and was considered unrelated to MRG-106. The remaining five patients have completed the dosing and follow-up periods. Adverse events for these patients noted by the treating physician as possibly or definitely related to MRG-106, included redness of the skin, pain, burning or tingling at the injection site, skin inflammation and a hand sore. All possibly or definitely related adverse events were judged as mild or moderate in severity. Abnormal lab values possibly related to use of the product candidate were observed in two patients and included moderate neutropenia and prolonged partial thromboplastin time, both of which resolved while continuing MRG-106.

In Part B of the clinical trial, three patients each in the 300 mg, 600 mg and 900 mg dose cohorts were to receive a total of six subcutaneous doses of MRG-106 administered over a 26-day period. All three dose levels were generally well tolerated in the eight patients that completed dosing. The treating physicians for these patients noted the following adverse events, which were possibly or definitely related to MRG-106: (i) five patients experienced mild to moderate pain or irritation at the site of injections on six occasions (ii) one patient experienced a rash at multiple injection sites; (iii) one patient experienced tenderness and bruising at multiple injection sites, as well as intermittent blurred vision (without objective evidence of visual disturbance upon examination by an ophthalmologist) and intermittent diarrhea; and (iv) one patient experienced redness of the skin around an injection site. One patient in the 900 mg dose cohort had worsening of their skin lesions associated with increased itching, which changed from mild to severe after receiving three doses of 900 mg. This patient stopped receiving MRG-106 and was treated with prednisone, and the patient's skin lesions and itching improved. No serious adverse events have been reported in Part B. Abnormal lab values possibly related to the administration of MRG-106 included mild, transient increases in liver enzymes in one patient dosed at the 600 mg dose level, transient increases in creatine kinase (an indicator of muscle stress) in one patient each at the 600 and 900 mg dose levels, increased creatinine and decreased lymphocyte count in one patient at the 900 mg dose level, and transient neutropenia in one patient dosed at the 900 mg dose level. The change in these lab values was transient during the course of dosing with MRG-106 and returned to normal by the end of the dosing period.

Pharmacokinetic analysis of the plasma collected from Part A of the clinical trial indicated that MRG-106 was quickly absorbed into the systemic circulation with the highest concentrations being observed 10 minutes to one hour after MRG-106 administration. Preliminary pharmacokinetic data from Part B of the clinical trial in the first nine patients dosed subcutaneously with 300 mg, 600 mg, or 900 mg of MRG-106 demonstrate this route of administration affects the time required to reach maximal concentrations of drug in the systemic circulation (approximately three to six hours) compared to intratumoral administration. Systemic exposure in the patients increased in a proportional manner to the increased dose levels administered.

In Part A of the clinical trial, high levels of MRG-106 (48 -204 µg per gram of tissue) were detected in injected tumors. We also observed accumulation of MRG-106 in a lesion distant from the site of injection at low levels (4 µg per gram of tissue). Preliminary analysis of injected tumors also indicated an increased expression of several direct targets of miR-155, suggesting that the drug is inhibiting its intended molecular target. The assessment of the pharmacodynamic effect of MRG-106 in skin lesions of Part B patients is ongoing.

Efficacy

All patients who received MRG-106 in Part A of the clinical trial demonstrated a beneficial clinical response. Intratumoral injection resulted in significant absorption in to the systemic circulation. Exploratory assessment of clinical response to therapy was performed for both MRG-106-treated and saline-treated lesions based on the change from baseline in the CAILS scores. Four of the five patients who completed dosing had their scores evaluated in the MRG-106 treated lesions. In the fifth patient, CAILS scores were monitored in two untreated lesions, instead of the treated lesions. The treated lesions in the four patients showed a 50% or greater reduction in the baseline CAILS score, which was maintained to the end of study visit (either 28 days or 35 days after the first dose). A greater than 50% reduction was observed in one saline injected lesion. The CAILS scores for patients in Part A of the clinical trial are set forth below.

Part A: Lesion CAILS

				MRG-106 Treated Lesions			Untreated or Saline Treated Lesions		
Patient Number	Number of Doses	Dose	Duration of Treatment (Days)	First CAILS Score	Lowest CAILS Score	Maximal % Reduction in CAILS	First CAILS Score	Lowest CAILS Score	Maximal % Reduction in CAILS
1 (early termination)	3	75 mg	9	18	12	33 %	18	14	22 %
2	4	75 mg	8	16	8	50 %	NA	NA	NA
3	4	75 mg	8	12	6	50 %	8	5	37 %
4 Lesion 1	4	75 mg	8	NA	NA	NA	15	8	47 %
4 Lesion 2	4	75 mg	8	NA	NA	NA	36	25	31 %

5	5	75 mg	15	26	6	77	%	20	5	75	%
6	5	75 mg	15	12	4	67	%	9	5	44	%

Histological examination of pre-treatment and post-treatment tumor biopsies of the same lesion injected with MRG-106 was conducted in five patients. At baseline, these biopsies typically showed evidence of cancer and high cancer cell density. After treatment, histology revealed fewer cancerous cells or a reduction in cancer cell density or depth in most patients. One patient who received MRG-106 injections in a small tumor showed a complete absence of cancerous T-cells in the post-treatment biopsy. Another patient had a lower percentage of CD30+ large atypical cells after MRG-106 treatment, which is indicative of a reduction in the number of cells with malignant characteristics.

Part B of the clinical trial has enrolled nine patients in the subcutaneous dosing cohorts, three in each of the 300 mg, 600 mg and 900 mg dose levels, eight of whom received six doses of MRG-106 over a 26-day period. Patients in the 300 mg and 600 mg dose cohorts have completed the clinical trial, including a follow-up visit on the 56th day of the clinical trial. Three patients completed the first cycle of dosing and then continued on to the optional extension part of the protocol; as of March 13, 2017, two of those three patients continued to receive MRG-106. The extension protocol provides continued observation of safety and clinical response for longer durations which may allow for a better understanding of potential adverse effects as well as beneficial dose and dose response.

Exploratory assessment of clinical response to therapy in Part B was performed by assessing the CAILS score for up to five lesions for each patient (one patient had only one lesion). The mSWAT and CAILS scores for each patient are shown in the table below. Two patients from the 300 mg dose group and one patient in the 600 mg dose group demonstrated reductions in their baseline mSWAT of 50% or greater and two of these patients also had reduction of 50% or greater in their CAILS scores. Additional patients have shown lesser improvements in CAILS and mSWAT scores as demonstrated in the table below.

Part B: CAILS and mSWAT

Patient Number	Number of Doses	Dose	Days on Trial Extension		Combined CAILS Score				mSWAT Score			
					First CAILS Score	Lowest CAILS Score	Maximal % Reduction in CAILS		First mSWAT Score	Lowest mSWAT Score	Maximal % Reduction in mSWAT	
1	6	300 mg	—		10	9	10	%	2	1	50	%
2	6	300 mg	—		40	10	75	%	47	23	51	%
3	6	300 mg	—		44	40	9	%	1.5	1.1	27	%
4	14	600 mg	60	**	45	21	53	%	22	10	55	%
5	6	600 mg	—		58	49	16	%	20.3	18.8	7	%
6	6	600 mg	—		82	70	15	%	42.7	40.1	6	%
7	13	900 mg	49	**	68	51	25	%	17.2	10	42	%
8	9	900 mg	44		18	21	NR		5.75	6.25	NR	
9	3	900 mg	—		*30	*34	*NR		*103	*97	*6	%

* Patient 9 received three doses prior to discontinuation of dosing.
** Days on trial extension as of March 13, 2017; patient dosing is ongoing.
NR No Reduction

Biomarker Analysis

Biomarkers were analyzed to assess the ability of MRG-106 to regulate the expression of gene pathways that are associated with elevated levels of miR-155 in MF. We identified a set of biomarkers based on MRG-106 activity in cell lines derived from MF patients. In Part A of the clinical trial, we assessed the expression of these biomarker genes in lesions before and after treatment with MRG-106. Retrospective analysis of a subset of the genes from the cell line data demonstrated that MRG-106 treatment decreased expression of some genes associated with cellular proliferation and increased expression of some genes associated with cell death. The expression of these genes appears to correspond to the level of drug measured in the lesion biopsy. We also believe these data illustrate the potential of its approach to identify molecular biomarkers that translate from pre-clinical studies to predict product candidate activity in clinical trials.

MRG-201

MRG-201 is a replacement for miR-29 that is intended to increase miR-29-like activity in the setting of fibrotic disease. We are currently studying MRG-201 in a single-center, Phase 1, double-blind, placebo-controlled, single and multiple dose-escalation clinical trial enrolling up to 70 healthy volunteers.

We believe that the miR-29 family of miRNAs is consistently present at abnormally low levels during fibrotic disease progression. We initially discovered the role of miR-29 in pathological cardiac fibrosis. Since this initial discovery, miR-29 has been implicated in pathological fibrosis in multiple organs including the skin, eye, lung, liver and kidney. miR-29 is understood by the scientific community to play a role in the regulation of certain processes that contribute to fibrosis, including the initiation and maintenance of fibrosis through transforming growth factor beta, or TGF-ß, signaling and the deposition of the components that make up fibrotic tissue, including collagen and extracellular matrix, or ECM, proteins. Furthermore, both fibrotic ECM and TGF-ß are believed to down-regulate miR-29 levels, leading to continuously increased TGF-ß expression and uncontrolled ECM production. miR-29 levels are abnormally low in multiple fibrotic indications, and lower levels of miR-29 are correlated with increased severity of fibrosis. Although various fibrotic indications are potentially distinct, they share a number of features, including the activation of the cells that initiate the deposition of fibrotic tissue or fibroblast activation, excessive deposition of collagen and other fibrosis-associated pathways, and resulting organ dysfunction. We believe the functions and biomarkers regulated by miR-29 might be shared among multiple fibrotic indications and increasing miR-29-like activity may provide potential benefit in any of these.

To demonstrate mechanistic proof-of-concept and as a potential initial indication, we are currently focused on skin fibrosis. We believe the data derived from skin fibrosis trials may facilitate development of a product candidate intended for the treatment for Idiopathic Pulmonary Fibrosis, or IPF, and other major organ pathological fibrosis.

There are three primary objectives that we intend to address prior to initiating a trial in a major organ fibrosis disease, such as lung or liver fibrosis:

- Demonstrate mechanistic proof of concept in humans for MRG-201. In our Phase 1 clinical trial of MRG-201, skin fibrosis was induced by making incisions in the volunteers' skin and biomarkers of fibrosis, including collagens and other fibrosis-associated genes were monitored to measure active gene regulation by MRG-201. Skin manifestation of pathological fibrosis, such as keloids that are abnormal proliferation of scar tissue that can form at the site of a skin injury and other forms of raised or hypertrophic scarring, may be an area in which we conduct additional development work, depending on the data from the Phase 1 clinical trial.
- Confirm the correlation of biological pathways between skin fibrosis and other major organ fibrosis. We have identified a subset of biomarker genes that we believe are regulated by MRG-201 in pre-clinical models of skin fibrosis, including mouse, rat, and rabbit, as well as in human skin fibroblasts in culture. This subset of biomarker genes includes multiple collagens and additional fibrosis-associated genes that appear to be implicated in fibrosis. The expression of these genes is generally increased in pathological fibrosis in humans, including skin fibrosis (an example of which is scleroderma) and pulmonary fibrosis (an example of which is IPF or systemic sclerosis). This gene signature appears to be regulated in common in skin fibrosis and IPF.

- Develop strategies for delivery of miR-29 replacements to allow for treatment of the lung and other major organs. We are collaborating with the Lovelace Respiratory Research Institute and a laboratory at Yale University under a grant from NIH to evaluate and develop potential inhaled delivery of MRG-201. Inhaled delivery has the potential to deliver more active drug to the lung. In pre-clinical models, we delivered MRG-201 to the lung and demonstrated reversal of pulmonary fibrosis in rodents which was induced by the administration of bleomycin, a chemotherapy agent known to induce lung fibrosis. In addition, MRG-201 was able to reduce pulmonary fibrosis that was induced in rodents by TGF-ß over-expression. Furthermore, a recently published study demonstrated the ability to reverse liver fibrosis in rodents through the use of an engineered virus that expresses miR-29. The viral expression of miR-29 in the study occurred in the chief functional cells of the liver. We have shown in pre-clinical testing that miR-29 replacements, delivered using two different methods reduced the expression of biomarkers of fibrosis in the post-exposure animal model of liver fibrosis induced by carbon tetrachloride. Finally, we believe injecting a miR-29 mimic into the eye may allow a local administration of MRG-201 to reduce retinal fibrosis.

Pathological Fibrosis

Fibrosis describes the development of fibrous connective tissue as a response to injury or damage. Fibrosis may refer to the deposition of connective tissue that occurs as part of normal healing or to the excess tissue deposition that occurs as a disease process. When fibrosis occurs in response to injury, the term “scarring” is used. Pathological fibrosis can occur in many tissues of the body as a result of inflammation or damage. In pathological fibrosis, collagen build up occurs, which can result in scarring of vital organs such as the skin, lung, liver, eye, kidney and heart leading to irreparable damage and eventual organ failure. We believe there is a significant need for additional clinically satisfactory therapeutic approaches to treating pathological fibrosis.

Below is a description of several types of pathological fibrosis that we may seek to develop a product candidate based on a replacement for miR-29:

Type of Pathological Fibrosis	Description
Skin Fibrosis	• Scarring is a result of an over production of collagen in a healing wound. Scarring may continue to thicken for up to six months or may overgrow the site of the wound, even after the wound has healed. • Hypertrophic scars and keloids are abnormal wound responses, and represent an excessive connective tissue response to skin trauma, inflammation, surgery, or burns. • Hypertrophic scars and keloids are characterized by local fibroblast proliferation and overproduction of collagen. Both hypertrophic scars and keloids are diseases that tend to be painful and itchy, restrict mobility, and are resistant to treatment.
Pulmonary Fibrosis	• Pulmonary fibrosis, also known as lung fibrosis, refers to a number of conditions that cause lung damage in the tissue between and supporting the air sacs or

interstitial tissue, followed by fibrosis and eventually loss of lung elasticity. These conditions lead to symptoms such as persistent cough, chest pain, difficulty breathing and fatigue. Pulmonary fibrosis may occur as a secondary condition in various other diseases, but in many cases the underlying cause is not clear, and is referred to as IPF.

- IPF is a chronic, progressive lung disease which ultimately leads to death in many of the patients. This condition causes scar tissue to build up in the lungs, which makes the lungs unable to transport oxygen into the bloodstream effectively.

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Type of Pathological Fibrosis	Description
Liver Fibrosis	• Liver fibrosis refers to the scar tissue and nodules that replace liver tissue and disrupt liver function. Major causes of liver fibrosis are alcohol, chronic hepatitis B virus, hepatitis C virus infection along with the metabolic disorders non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Liver fibrosis is a major global problem driven by increasing rates of obesity and diabetes.
Eye Fibrosis	• Infection or inflammation of the eye results in impairment of visual function. Chronic inflammation can ultimately lead to fibrosis. • Eye fibrosis diseases include retinal fibrosis such as diabetic retinopathy and proliferative vitreoretinopathy, corneal fibrosis, glaucoma trabeculectomy, age related macular degeneration, and Fuch's endothelial corneal dystrophy.

MRG-201 Phase 1 Clinical Trial

Trial Design

We are conducting a single-center Phase 1, double-blind, placebo-controlled, single and multiple dose-escalation clinical trial of MRG-201. MRG-201 is designed to mimic the activity of a molecule called miR-29 that has been shown to decrease the expression of collagen and other proteins that are involved in scar formation. MRG-201 is being studied to determine if it can limit the formation of fibrous scar tissue that leads to pathologic fibrosis. This four-part clinical trial is expected to enroll up to 70 healthy volunteers in which:

- Part A studied the expression of biomarker genes in skin at different time points following an incision, and was performed without product candidate administration;
- Part B studied a single ascending dose of 0.5 to 14 mg of MRG-201 in intact skin;
- Part C studied a single ascending dose of 4, 7 or 14mg of MRG-201 administered around skin incisions; and
- Part D is studying multiple ascending doses of MRG-201 ranging from 4 mg to 14 mg administered around skin incisions.

The primary objectives in this clinical trial are safety and tolerability of MRG-201 injected into the skin via intradermal injections. A secondary objective is to characterize local skin and systemic exposure to MRG-201 following intradermal injection. Exploratory endpoints include the pharmacodynamic effects of MRG-201 on the

expression of miR-29 gene targets in skin wound biopsies and to evaluate changes in histology from skin wounds treated with MRG-201.

Safety and Pharmacokinetics

As of March 13, 2017, 54 volunteers have participated in the clinical trial, 47 of whom have been administered MRG-201 and seven of whom have been incised without receiving a dose of MRG-201.

Nineteen volunteers in Part B received a single dose of 0.5 mg, 1 mg, 2 mg, 4 mg, 7 mg or 14 mg of MRG-201 in unincised skin. In these volunteers, MRG-201 was generally well tolerated. Three incidents of injection site reactions were reported, which were generally moderate. Additional adverse events of mild severity were reported as possibly related to receiving MRG-201, and included redness of the skin, a tingling sensation and sensations of warmth at a patient's injection site, and sensations of warmth on a patient's limbs and back, all of which resolved within 24 hours, as well as fatigue, which resolved in less than a week.

Nine volunteers in Part C received a single dose of either 4 mg, 7 mg or 14 mg of MRG-201 around an incision (three volunteers per group). In these volunteers, MRG-201 was generally well tolerated at all dose levels evaluated. One incident of injection site reaction was reported, which was moderate and resolved within approximately 48 hours.

Nine volunteers in the dose-escalation portion of Part D received six total doses each of 4 mg, 7 mg or 14 mg of MRG-201 around an incision. In these volunteers, MRG-201 was generally well tolerated at all dose levels evaluated. There were two injection site reactions of moderate severity reported. Five adverse events of mild severity reported by the treating physicians as possibly or definitely related to receiving MRG-201 included itching or pain at the injection site, fatigue, headache, and microscopic hematuria (blood in the urine), which had all resolved by the end of the study.

An additional 10 volunteers were enrolled in Part D to understand drug diffusion. Volunteers received six total doses each of 14 mg of MRG-201 at one end of a 4 cm incision. The other end of the incision is untreated. Both ends of the incision will be biopsied to measure the potential for diffusion and pharmacodynamic activity of MRG-201 away from the site of injection. In these volunteers, MRG-201 was generally well tolerated at all dose levels evaluated. One volunteer had an injection site reaction of mild severity and one had an injection site reaction of moderate severity. Three adverse events of mild severity reported by the treating physicians as possibly related to receiving MRG-201 included chills, weakness, and localized edema and itchiness around a patient's injection site.

Preliminary pharmacokinetic analysis of plasma collected from the MRG-201 volunteers in Part B, Part C, and Part D (data available for first 12 subjects only) of the clinical trial revealed that very little drug (less than 150 ng/mL) is generally detectable in the blood when MRG-201 is injected intradermally into the skin.

Biomarker Analysis and Histopathology

In Part A of the clinical trial in which volunteers were incised without receiving any product candidate or placebo, molecular analysis confirmed that miR-29 expression decreased in incised skin compared to unincised skin, as expected for fibrosis. In addition, gene expression of miR-29/MRG-201 biomarkers, including collagens and fibrosis-related genes, was increased approximately two-to-20-fold in incised skin, and was correlated with the decrease in miR-29 expression. The magnitude of the change in the expression of miR-29 and the biomarker genes was approximately 30-85% greater 16 days after administration than it was nine days after administration, indicating a time-dependent effect on gene expression. We believe these data indicate the role of miR-29 in potentially regulating the biological pathways implicated in fibrosis in human skin.

In Part C of the clinical trial, biomarkers were analyzed to assess the ability of MRG-201 to regulate the expression of genes that are associated with reduced miR-29 expression in human skin. We identified a set of biomarkers based on MRG-201 activity in pre-clinical models of skin fibrosis, including mouse, rat, and rabbit skin in vivo, as well as human skin fibroblasts in vitro. The biomarker panel consists of direct targets for miR-29 and downstream genes we believe are indicative of an impact on miR-29 expression in wound healing and fibrosis, particularly collagens and other genes important in fibrosis. We assessed the expression of these biomarkers in biopsies taken from the site of the incision 24 hours after a single MRG-201 dose compared to saline-treated lesions. Analysis of the biomarker data indicated that MRG-201 decreased expression of collagens and fibrosis-associated genes, consistent with the role we believe miR-29 plays in regulating these fibrosis-related genes. The change in expression of collagens and fibrosis-related genes appeared to be correlated with the amount of MRG-201 administered. We believe these data demonstrate an effect of MRG-201 on fibrosis-associated genes, and provide an indication that MRG-201 has the potential to reduce fibrosis and scar formation in human skin. We also believe these data highlight the potential of our approach to identify molecular biomarkers that translate from pre-clinical studies to assessing the activity of MRG-201 in human clinical trials.

Part D of the clinical trial is currently in progress. Three cohorts of three volunteers each received six total doses of 4 mg, 7 mg or 14 mg of MRG-201 and have completed dosing and the follow-up process, and a final cohort of 10 volunteers are undergoing dosing and follow up at the 14 mg dose level. Based on biomarker analysis, the collagen and fibrosis-related genes were decreased in eight of the nine drug-treated incisions compared to the saline control that have been analyzed to date. Additionally, histological analysis indicated that incisions treated with multiple administrations of MRG-201 showed a statistically significant reduction in the area and depth of fibroplasia, a marker of fibrosis or scar formation. Furthermore, we observed that the magnitude of fibroplasia prevention corresponds to the magnitude of biomarker regulation. We believe these data may suggest that MRG-201 has the potential to reduce fibrosis and scar formation in human skin. The collagens and extracellular matrix genes regulated by MRG-201 in human skin have also been implicated in pulmonary fibrosis, including IPF. We believe the molecular and histological

data for MRG-201 in human skin support additional development of a miR-29 mimic for IPF and additional fibrotic indications.

MRG-201 Pre-Clinical Activities

Correlation of Biological Pathways Between Skin Fibrosis and Other Major Organ Fibrosis

The biomarkers that we believe are regulated by MRG-201 in human skin represent biological pathways that are associated with skin fibrosis, but are also fundamental processes involved in pathologic fibrosis in general. Increased expression of collagens and additional fibrosis-associated genes that we believe are down-regulated by MRG-201 have been associated with multiple fibrotic indications, including scleroderma, keloids, hypertrophic scarring, IPF, systemic sclerosis, pulmonary fibrosis, fibrosis of the eye (retinal and corneal fibrosis), kidney fibrosis, and cardiac fibrosis. We believe the that the documented ability of MRG-201 to reduce the expression of these fibrosis-associated biomarkers in human skin suggests that a miR-29 mimic could also provide anti-fibrotic activity in multiple fibrotic indications.

Work done by us, as well as published data indicate that a set of biomarkers showing increased expression in response to incision-induced fibrosis in human skin also show increased expression in multiple fibrotic indications including pulmonary fibrosis.

Delivery of miR-29 Mimic to the Lung

Together with Yale University and Lovelace Respiratory Research Institute, we were awarded a Centers for Advanced Diagnostics and Experimental Therapeutics in Lung Disease Stage II Grant from the NIH in 2014. The objective of the grant is to develop miR-29 mimicry as an efficient and personalized anti-fibrotic therapy. The collaboration is currently in year three of the five-year grant. During the first two years of the grant, the group compared intravenous and aerosolized delivery routes for the amount of miR-29 mimic that enters circulation, distribution, pharmacokinetics, pharmacodynamics, and efficacy. In one of its laboratories, Yale University also established a blood assay for miR-29 detection in IPF patients. During years three through five of the grant, we plan to perform potential IND-enabling activities including additional development of an aerosolized formulation and dose of miR-29 mimic, good manufacturing practice, or GMP, manufacturing of the product candidate, and complete good laboratory practice, or GLP, toxicology studies. In addition, the collaboration plans to further develop its blood miR-29 diagnostic and assess correlations to tissue and lung cells collected through a procedure called bronchoalveolar lavage.

Delivery of miR-29 Mimic to the Liver

miR-29 family members are expressed at less than normal levels in pre-clinical models of liver fibrosis as well as in biopsies from human fibrotic livers. Delivery of miR-29 to liver cells using Adeno-Associated Virus, or AAV, has been shown to reverse liver fibrosis induced by carbon tetrachloride in a rodent model. We are currently assessing liver delivery of several miR-29 replacements with varying conjugates. Initial data from such assessments has shown liver delivery in rodent models. We are studying multiple compounds in an efficacy study in rodents with the AAV-delivered miR-29 in a carbon tetrachloride model of liver fibrosis. We believe the results of these studies will assist our potential compound selection for IND-enabling activities with novel miR-29 replacements or the use of AAV for the delivery of miR-29 in hepatic fibrosis.

Delivery of miR-29 Mimic to the Eye

We are exploring miR-29 as a therapeutic for ocular indications including ocular fibrosis. RNA-based therapeutics can be administered to the eye via eye drops for diseases affecting the front of the eye (e.g., the cornea and anterior chamber), and via injection into the eye for diseases affecting the back of the eye (which is commonly referred to as the retina). Both routes of administration have been established to be generally well-tolerated for oligonucleotide therapeutics. We believe that the direct application of our microRNA therapeutic candidate to the eye may have the advantage of a greater than one-week duration, as the posterior chamber of the eye is a closed compartment, and is devoid of the usual clearance mechanisms present in the rest of the body. Historically, this mode of drug delivery potentially allows infrequent dosing, and also provides the potential advantage of reduced systemic exposure. Preliminary pre-clinical studies investigated direct injection into the eye of a double-stranded RNA molecule structurally similar to the design of MRG-201, and demonstrated decreased expression of the targeted gene. These data demonstrated functional delivery of double-stranded RNA molecules to the retina in the absence of a delivery vehicle.

Cardiovascular Disease

We are also developing RNA-based therapeutics in three cardiovascular programs through our collaboration with Servier. Under this collaboration, we granted Servier exclusive licenses to commercialize three cardiovascular product candidates in all countries except the United States and Japan. Servier may fund development through Phase 2 clinical trials, while we retain all commercial rights to these programs in the United States and Japan.

We have additional pre-clinical cardiovascular programs in which it is collaborating with academic institutions. In 2015, we were designated as a collaborating institution for a grant that provides more than €2 million over a three-year period (2015-2017) funded by the German Federal Ministry of Education and Research.

Other Pre-Clinical Programs

In 2016, we were awarded a milestone-driven grant by The ALS Association of up to $0.4 million to advance the development of MRG-107. MRG-107 is an inhibitor of miR-155 intended to be developed for the treatment of amyotrophic lateral sclerosis, or ALS.

We are also evaluating and developing additional microRNA-targeted, pre-clinical product candidates in a variety of disease indications where an abnormal level of one or more microRNAs has been implicated in disease pathology. Our inhibitor programs, including these product candidates, were created using the locked nucleic acid technology that we exclusively licensed from Santaris Pharma A/S (now a wholly-owned subsidiary of F. Hoffmann-La Roche Ltd, or Roche), on a target-by-target basis. We believe combining this technology with our internal expertise may allow us to create unique product candidates that possess desirable drug-like properties capable of entering diseased cells without the need for additional delivery technologies. We have a broad patent portfolio intended to protect these product candidates.

Background on microRNA

microRNAs are transcribed from the genome and unlike messenger RNA, or mRNA, they do not encode proteins. microRNAs function by preventing the translation of mRNAs into proteins and/or by triggering degradation of these mRNAs. Studies have shown that microRNA gene regulation is often not a decisive on and off switch but a subtle function that fine-tunes cellular phenotypes that becomes more pronounced during stress or disease conditions. microRNAs were first discovered in 1993 and have since been found in nearly every biological system examined since that time. They are highly conserved across species, demonstrating their importance to biological functions and cellular processes. According to the Sanger Institute, over 1,000 microRNAs have been identified in humans.

A body of evidence has shown that inappropriate levels of particular microRNAs are directly linked to a range of serious diseases, many of which are poorly served by existing therapies. microRNAs can affect the balance of protein expression and serve as “command and control” nodes that directly coordinate multiple critical systems simultaneously. This effect on systems biology is a naturally occurring homeostatic process that becomes disrupted in certain disease states. As a result, developing microRNA therapeutics is fundamentally different from the single-protein, single-target approach that is the foundation of traditional small and large molecule drugs.

Our Approach to Drug Discovery and Development

We believe that our drug discovery and development strategy will enable us to progress our product candidates from pre-clinical discovery to achievement of a plausible link to clinical benefit in humans relatively quickly and efficiently. In supporting this strategy, we incurred $13.7 million and $13.3 million in research and development activities for the years ended December 31, 2016 and 2015, respectively.

Discovery

Although there are over 1,000 identified human microRNAs, not all of them have been shown to be causal in disease. Our approach to drug discovery and development begins with the identification of potentially pathological microRNAs.

We apply three general approaches to the identification of potentially pathological, or disease causing, microRNAs (i) profiling of microRNA expression in diseased tissue versus normal tissue to identify microRNAs that are found at abnormally high or low levels (ii) identification of microRNAs that are located within genes (typically in non-protein coding segments) of validated disease relevant genes and thus simultaneously expressed with the disease associated gene and (iii) evaluation of microRNAs that are predicted to directly modulate the expression of specific disease relevant genes.

We have focused our programs to develop therapeutic microRNA inhibitors as opposed to microRNA replacements. We believe the inhibitor candidates face lower delivery hurdles and have better drug-like properties in regards to affinity to their target, stability, drug distribution and pharmacodynamics. To improve their therapeutic potential, we chemically modify these compounds with changes such as locked nucleic acid (known as LNA) substitution of the ribose sugar in many of the nucleosides and deoxyribonucleoside (known as DNA).

In conditions where a deficit in microRNA expression has been identified as disease causing, microRNA replacements, which are modified double-stranded RNA structures that are recognized by the RNA-induced silencing complex, or RISC, can serve as chemically synthesized replacements for microRNAs.

Historically, the delivery of double stranded RNAs, such as microRNA replacements, has been a significant hurdle to overcome for drug development because these molecules are very rapidly degraded, and because uptake into cells can be inefficient. Our delivery approach for microRNA replacements is to append a conjugate to the molecule to enhance cellular uptake. The selection of the conjugate is dependent on the intended therapeutic use. We have deployed

hydrophobic conjugates, such as cholesterol that are able to improve pharmacokinetics and allow for enhanced cellular uptake. We are also exploring a range of conjugates that help in targeting specific tissues and cells. Our strategy with microRNA replacements has centered on opportunities for efficient delivery of the molecules with an emphasis on local and topical applications, such as injections in the skin or lung, respectively. For organs where topical or local applications are not feasible, such as the liver, we have employed conjugates that have demonstrated successful delivery after systemic administration.

Development

Our approach to translational medicine is focused on rapidly testing the molecular hypothesis in human cell lines and animal models to demonstrate safety and measure pharmacokinetics and pharmacodynamics, and finally designing and conducting small, efficient and targeted human Phase 1 clinical trials. We typically select an initial indication that is genetically defined or is a rare disease where abnormal levels of a microRNA have been implicated. These early stage Phase 1 clinical trials are designed to test the mechanistic relevance or develop mechanistic proof-of-concept in humans in a setting that provides the opportunity to develop a biomarker toolkit for a mechanism of action that we believe has broader disease relevance.

The mechanistic proof-of-concept studies are designed to provide relevant information that helps to reduce development risks in humans. Our aim is to demonstrate that the expression levels of the microRNA could potentially serve as a diagnostic indicator that allows for better patient selection for later clinical trials and in additional indications. At the same time, we seek to confirm molecular activity of the drug.

By measuring the pharmacodynamics of target engagement, we are able to show that the product candidate effectively enters the appropriate cell and binds to its intended target. This process is particularly important for oligonucleotide drugs. We can also measure the effects on a series of downstream genes that create a plausible link between target engagement and a mechanism of disease.

For some diseases, we believe that local administration allows it to achieve a variety of concentrations of drug at the site of action and facilitates the development of dose / response relationships. We believe understanding the dose necessary to show target engagement, with concomitant surrogate marker alterations provides the basis for which a systemic dose can be defined that will be necessary to potentially achieve a therapeutic effect.

Exploratory endpoints can provide us with verification of the pharmacodynamic effects of the drug based on biomarker readouts and morphological alterations. This translational strategy allows us to answer many questions about the drug target pair and provides improved confidence that the molecular basis of drug action is relevant in humans. Having built confidence in the drug mechanism and demonstrated an acceptable safety profile, later stage clinical trials will be designed to establish appropriate dose and therapeutic efficacy.

Our Strategic Collaborations and License Agreements

Strategic Alliance and Collaboration with Servier

In October 2011, we entered into a strategic alliance with Servier for the research, development, and commercialization of RNA-targeting therapeutics in cardiovascular disease, or the Servier Collaboration Agreement, which was subsequently amended in May 2013, May 2014, May 2015 and September 2016. Under the Servier Collaboration Agreement, we granted Servier an exclusive license to research, develop, and commercialize RNA-targeting therapeutics for three targets in the cardiovascular field. As of December 31, 2016, three named targets exist under the Servier Collaboration Agreement.

Servier's rights to each of the targets are limited to therapeutics in the cardiovascular field in their territory, which is worldwide except for the United States and Japan. We retain all rights for each named target in the United States and Japan.

In connection with entering into the strategic alliance with Servier, we received a nonrefundable upfront payment of $8.4 million (€6.0 million) in 2011 and an additional $4.0 million (€3.0 million) in 2013 when Servier exercised their right to name a third target under the agreement. We are also eligible to receive development milestone payments of €5.8 million to €13.8 million ($6.1 million to $14.5 million as of December 31, 2016) and regulatory milestone payments of €10.0 million to €40.0 million ($10.5 million to $42.1 million as of December 31, 2016) for each target. Additionally, we may receive up to €175 million ($184.1 million as of December 31, 2016) in commercialization milestones as well as quarterly royalty payments between the low-double digits to the mid-teens (subject to reductions for patent expiration, generic competition, third-party royalty and costs of goods) on the net sales of any licensed product commercialized by Servier. Additionally, if we undergo a change of control in specified circumstances, Servier has agreed to increase this royalty by up to an additional percentage in the low-single digits if it seeks to obtain an exclusive license to certain of the acquirer's intellectual property for the development and sales of product candidates under the Servier Collaboration Agreement. Servier is obligated to make any such royalty payment for a specified period under the Servier Collaboration Agreement.

As part of the Servier Collaboration Agreement, we established a multiple-year research collaboration, under which we jointly perform agreed upon research activities directed to the identification and characterization of named targets and oligonucleotides in the cardiovascular field, which we refer to as the Research Collaboration. The initial three-year term of the Research Collaboration was extended by two additional years in May 2014 and again by one additional year in September 2016 through October 2017. Servier is responsible for funding all of the costs of the Research Collaboration, as defined under the Servier Collaboration Agreement. During the years ended December 31, 2016 and 2015, we recognized as revenue amounts reimbursable to us under the Servier Collaboration Agreement for research and development activities of $2.3 million and $3.8 million, respectively.

The development of each product candidate (commencing with registration enabling toxicology studies) under the Servier Collaboration Agreement is performed pursuant to a mutually agreed upon development plan to be conducted by the parties as necessary to generate data useful for both parties to obtain regulatory approval of such product candidates. Servier is responsible for a specified percentage of the cost of research and development activities under the development plan through the completion of one or more Phase 2 clinical trials and will reimburse us for a specified portion of such costs that we incur. The costs of Phase 3 clinical trials for each product candidate will be allocated between the parties at one of several specified percentages of costs. The applicable percentage for each product candidate will be based upon whether certain events under the Servier Collaboration Agreement occur, including if we enter into a third-party agreement for the development and/or commercialization of the product in the United States at least 180 days before the initiation of the first Phase 3 clinical trial or if we subsequently enter into a U.S. partner agreement or if we do not enter into a U.S. partner agreement, but file for approval in the United States using data from the Phase 3 clinical trial. We are responsible, by ourself or through a third-party manufacturer, for the manufacture and supply of all licensed oligonucleotides during the pre-clinical phase of development under the Sevier Collaboration Agreement while Servier is primarily responsible for manufacture and supply of all licensed oligonucleotides and product during the clinical phase of development under the Servier Collaboration Agreement. Each party is responsible for the commercial supply of any licensed product to be sold in its territory under the Servier Collaboration Agreement.

Under the Servier Collaboration Agreement, we also granted Servier a royalty-free, non-exclusive license to develop a companion diagnostic for any therapeutic product which may be developed by Servier under the Servier Collaboration Agreement. We also granted Servier an exclusive, royalty free license to commercialize such a companion diagnostic in our territory for use in connection with the development and commercialization of such therapeutic product in its territory.

The Servier Collaboration Agreement will expire as to each underlying product candidate when Servier’s royalty obligations as to such product candidate have expired. Servier may also terminate the Servier Collaboration Agreement for (i) convenience upon a specified number of days’ prior notice to us or (ii) upon determination of a safety issue relating to development under the agreement upon a specified number of days’ prior notice to us. Either party may terminate the Servier Collaboration Agreement upon a material breach by the other party which is not cured within a specified number of days. We may also terminate the agreement if Servier challenges any of the patents licensed by us to Servier.

License Agreements with the University of Texas

As of December 31, 2016, we had five exclusive patent license agreements, or the UT License Agreements, with the Board of Regents of The University of Texas System, or the University of Texas. Under each of the UT License Agreements, the University of Texas granted us exclusive and nonexclusive licenses to certain patent and technology rights. The University of Texas is one of our minority stockholders.

In consideration of rights granted by the University of Texas, we agreed to (i) pay a nonrefundable upfront license documentation fee in the amount of $10 thousand per license, (ii) pay an annual license maintenance fee in the amount of $10 thousand per license starting one year from the date of each agreement, (iii) reimburse the University of Texas for actual costs incurred in conjunction with the filing, prosecution, enforcement, and maintenance of patent rights prior to the effective date, and (iv) bear all future costs of and manage the filing, prosecution, and maintenance of patent rights. In 2016 and 2015, we incurred upfront and maintenance fees under the UT License Agreements totaling $0.1 million, and recorded the amounts as research and development expense. All costs related to the filing, prosecution, enforcement, and maintenance of patent and technology rights are recorded as general and administrative expense when incurred.

Under the terms of the UT License Agreements, we may be obligated to make the following future milestone payments for each licensed product candidate: (i) up to approximately $0.6 million upon the initiation of defined clinical trials, (ii) $2.0 million upon regulatory approval in the United States, and (iii) $0.5 million per region upon regulatory approval in other specified regions. Additionally, if we or our sublicensees successfully commercializes any product candidate subject to the UT License Agreements, we are responsible for royalty payments in the low-single digits based upon net sales of such licensed products and payments at a percentage in the mid-teens of any sublicense income, subject to specified exceptions. UT's right to the royalty payments will expire as to each license agreement upon the expiration of the last patent claim subject to the applicable UT License Agreement.

The license term extends on a product by product and country by country basis until the expiration of the last to expire of the licensed patents that covers such product in such country. Upon expiration of the royalty payment obligation, we will have a fully paid license in such country. We may also terminate each UT License Agreement for convenience upon a specified number of days' prior notice to the University of Texas. The University of Texas also has the right to earlier terminate the UT License Agreements after a defined date under specified circumstances where we have effectively abandoned our research and development efforts or have no sales. The UT License Agreements will terminate under customary termination provisions including automatic termination upon our bankruptcy or insolvency, upon notice of an uncured material breach, and upon mutual written consent. We have expensed all charges incurred under the UT License Agreements to date, due to the uncertainty as to future economic benefit from the acquired rights.

License Agreement with Roche Innovation Center Copenhagen A/S (formerly Santaris Pharma A/S)

In June 2010, we entered into a license agreement with the Santaris Pharma A/S, which subsequently changed its name to Roche Innovation Center Copenhagen A/S, or RICC, which was subsequently amended in October 2011 and amended and restated in December 2012, or the RICC License Agreement. In 2014, Santaris Pharma A/S was acquired by Roche and has become a wholly-owned subsidiary of Roche.

Under the RICC License Agreement, we received exclusive and nonexclusive licenses from RICC to use specified technology of RICC, or the RICC Technology, for specified uses including research, development, and commercialization of pharmaceutical products using this technology worldwide. Under the RICC License Agreement, we have the right to develop and commercialize the RICC Technology directed to four specified targets and the option to obtain exclusive product licenses for up to six additional targets. The acquisition of Santaris Pharma A/S by Roche was considered a change-of-control under the RICC License Agreement, and as such, certain terms and conditions of the RICC License Agreement changed, as contemplated and in accordance with the RICC License Agreement. These changes primarily relate to milestone payments reflected in the disclosures below. As consideration for the grant of the license and option, we previously paid RICC $2.3 million and issued RICC 856,806 shares of our Series A convertible preferred stock, which are now owned by Roche Finance Ltd, an affiliate of Roche, and, in 2017, were converted into 602,420 shares of our common stock as a result of the Merger. If we exercise our option to obtain additional product licenses or to replace the target families, we will be required to make additional payments to RICC.

Under the terms of the RICC License Agreement, milestone payments were previously decreased by a specified percentage as a result of the change of control by RICC referenced above. We are obligated to make future milestone payments for each licensed product for up to $5.2 million, which is inclusive of a potential product license option fee. Certain of these milestones will be increased by a specified percentage if we undergo a change in control during the term of the RICC License Agreement. If we grant a third party a sublicense to the RICC Technology, we are required to remit to Roche a specified percentage of the upfront and milestone and other specified payments that we receive under its sublicense, and if such sublicense covers use of the RICC Technology in the United States or the entire European Union, we will not have any further obligation to pay the fixed milestone payments noted above.

If we or our sublicensee successfully commercializes any product candidate subject to the RICC License Agreements, then RICC is entitled to royalty payments in the mid-single digits on the net sales of such product, provided that if such net sales are made by a sublicensee under the RICC License Agreement, RICC is entitled to royalty payments equal to the lesser of a percentage in the mid-single digits on the net sales of such product or a specified percentage of the royalties paid to us by such sublicensee, subject to specified restrictions. We are obligated to make any such royalty payments until the later of (i) a specified anniversary of the first commercial sale of the applicable product or (ii) the expiration of the last valid patent claim licensed by RICC under the RICC License Agreement underlying such product. Upon the occurrence of specified events, the royalty owed to RICC will be decreased by a specified percentage.

The RICC License Agreement will terminate upon the latest of the expiration of all of RICC's royalty rights, the termination of the last Miragen target or the expiration of its right to obtain a product license for a new target under the RICC License Agreement. We may also terminate the RICC License Agreement for convenience upon a specified number of days' prior notice to RICC, subject to specified terms and conditions. Either party may terminate the RICC License Agreement upon an uncured material breach by the other party and RICC may terminate the RICC License Agreement upon the occurrence of other specified events immediately or after such event is not cured within a specified number of days, as applicable.

License Agreements with the t2cure GmbH

In October 2010, we entered into a license and collaboration agreement, or the t2cure Agreement, with t2cure GmbH, or t2cure, which was subsequently amended in July 2014. Under the t2cure Agreement, we received a worldwide, royalty bearing, and exclusive license to specified patent and technology rights to develop and commercialize product candidates targeted at miR-92.

In consideration of rights granted by t2cure, we paid a onetime upfront fee of $46 thousand and agreed to: (i) pay an annual license maintenance fee in the amount of €3 thousand ($3 thousand at December 31, 2016), and (ii) reimburse t2cure for 100% of actual costs incurred in conjunction with the filing, prosecution, enforcement, and maintenance of patent rights. All costs related to the filing, prosecution, enforcement, and maintenance of patent and technology rights are recorded as general and administrative expense when incurred.

Under the terms of the t2cure Agreement, we are obligated to make the following future milestone payments for each licensed product: (i) up to approximately $0.7 million upon the initiation of certain defined clinical trials, (ii) $2.5 million upon regulatory approval in the United States and (iii) up to $1.5 million per region upon regulatory approval in the European Union or Japan. Additionally, if we or our sublicensees successfully commercialize any product candidate subject to the t2cure Agreement, we are responsible for royalty payments in the low-single digits upon net sales of licensed products and sublicense fees equal to a percentage in the low-twenties of sublicense income received by us. We are obligated to make any such royalty payment until the later of (i) the tenth anniversary of the first

commercial sale of the applicable product or (ii) the expiration of the last valid claim to a patent licensed by t2cure under the t2cure Agreement covering such product. If such patent claims expire prior to the end of the ten-year term, then the royalty owed to t2cure will be decreased by a specified percentage. We also have the right to decrease our royalty payments by a specified percentage for royalties paid to third parties for licenses to certain third-party intellectual property.

The license term extends on a country by country basis until the later of: (i) the tenth anniversary of the first commercial sale of a licensed product in a country, and (ii) the expiration of the last to expire valid claim that claims such licensed product in such country. Upon expiration of the royalty payment obligation, we will have a fully paid license in such country. We have the right to terminate the t2cure Agreement at will, on a country-by-country basis, after 60 days' written notice. The t2cure Agreement will also automatically terminate upon our bankruptcy or insolvency or upon notice of an uncured material breach.

Patent License Agreement with The Brigham and Women's Hospital

In May 2016, we entered into an exclusive patent license agreement, or the BWH License Agreement, with The Brigham and Women's Hospital, or BWH.

Under the BWH License Agreement, BWH granted us an exclusive, worldwide license, including a right to sublicense, to specified patent rights and a non-exclusive, worldwide license, including a right to sublicense, to specified technology of BWH. As consideration for this license, we paid BWH a specified issue fee and are obligated to pay a specified annual license fee. BWH is also entitled to milestone payments of up to approximately $2.6 million for each of our product candidates developed based on the patent rights subject to the BWH License Agreement plus a one-time sales milestone payment of $0.25 million for all product candidates developed based on the patent rights subject to the BWH License Agreement. If we successfully commercialize any product candidate subject to the BWH License Agreement, then BWH is entitled to royalty payments in the low-single digits on the net sales of such product. BWH's right to these royalty payments will expire on a product by product and country by country basis upon the expiration of the last patent claim in such country that is subject to BWH License Agreement and covers the product, and our license to such product in such country will become fully paid at such time. BWH is also entitled to a percentage in the low-double digits of any sublicense income from such product, subject to specified exceptions. We are also responsible for all costs associated with the preparation, filing, prosecution and maintenance of the patent rights subject to the BWH License Agreement.

Additionally, we are obligated to use commercially reasonable efforts to develop a product under the BWH License Agreement and to meet specified diligence milestones thereunder.

The BWH License Agreement will terminate upon the expiration of all issued patents and patent applications subject to the patent rights under the agreement. We may also terminate the BWH License Agreement for convenience upon a specified number of days' prior notice to BWH. BWH may terminate the BWH License Agreement upon a breach by us of our payment obligations and upon the occurrence of other specified events that are not cured within a specified number of days, provided that such termination is automatic upon our bankruptcy or insolvency.

Subcontract Agreement with Yale University

In October 2014, we entered into a subcontract agreement in October 2013 and into a subaward agreement in March 2015 with Yale, or the Yale Agreements. The subaward agreement was subsequently amended in February 2016, November 2016 and January 2017. Under the Yale Agreements, we agreed to provide specified services regarding the development of a proprietary compound that targets miR-29 in the indication of idiopathic pulmonary fibrosis. Yale entered into the Yale Agreements in connection with a grant that Yale received from the NIH for the development a miR-29 mimicry as a potential therapy for pulmonary fibrosis.

In consideration of our services under the Yale Agreements, Yale has agreed to pay us up to $1.1 million over five years. Under the terms of the Yale Agreements, we retain all rights to any and all intellectual property developed solely by us in connection with the Yale Agreements. Yale has also agreed to provide us with an exclusive option to negotiate in good faith for an exclusive, royalty-bearing license from Yale for any intellectual property developed by Yale or jointly by the parties under the Yale Agreements. Yale is responsible for filing, prosecuting and maintaining foreign and domestic patent applications and patents on all inventions jointly developed by the parties under the Yale Agreements.

The Yale Agreements terminates automatically on the date that Yale delivers its final research report to the NIH under the terms of the grant underlying the Yale Agreements. Each party may also terminate the Yale Agreements upon a specified number of days' notice in the event that the NIH's grant funding is reduced or terminated or upon material breach by the other party.

Manufacturing

We do not own or operate manufacturing facilities for the production of MRG-106, MRG-201 or other product candidates that we develop, nor do we have plans to develop our own manufacturing operations in the foreseeable future. We currently depend on third-party contract manufacturers for all of our required raw materials, active pharmaceutical ingredients, and finished product candidates for our clinical trials. We do not have any current contractual arrangements for the manufacture of commercial supplies of MRG-106, MRG-201 or any other product candidates that we develop. We currently employ internal resources and third-party consultants to manage our manufacturing contractors.

Sales and Marketing

We have not yet defined our sales, marketing or product distribution strategy for MRG-106, MRG-201 or any of our other product candidates because our product candidates are still in pre-clinical or early-stage clinical development. Our commercial strategy may include the use of strategic partners, distributors, a contract sale force, or the establishment of our own commercial and specialty sales force. We plan to further evaluate these alternatives as we approach approval for one of our product candidates.

Intellectual Property

We are actively building an intellectual property portfolio around our clinical-stage product candidates and discovery programs. A key component of this portfolio strategy is to seek patent protection in the United States and in major market countries that we consider important to the development of our business worldwide. As of February 28, 2017, we had a portfolio of 217 patents and patent applications of which 113 are issued or allowed and 104 are pending applications. This portfolio includes methods of use and composition patents, and patent applications on our two lead product candidates, MRG-106 and MRG-201. Our success depends in part on our ability to obtain and maintain proprietary protection for our product candidates and other discoveries, inventions, trade secrets and know-how that are critical to our business operations. Our success also depends in part on our ability to operate without infringing the proprietary rights of others, and in part, on our ability to prevent others from infringing our proprietary rights. A comprehensive discussion on risks relating to intellectual property is provided under "*Risk Factors*" under the subsection "*Risks Related to our Intellectual Property*".

We have filed composition of matter patent applications covering MRG-106 in June of 2016 in the United States as U.S. 15/173,368 and a PCT application as PCT/US2016/035865 to access foreign countries.

We expect this U.S. patent will issue in the next two to three years with an expiration year of 2036 if we continue to pay the maintenance fees and annuities when due, with the possibility of additional terms from the USPTO prosecution delays and from patent term extensions that may be granted due to administrative delays in the FDA. We also have pending applications that cover methods of administration and therapeutic uses of MRG-106 and related compositions. Collectively, these patents, if they issue, would have patent expirations from 2036 if we continue to pay the maintenance fees and annuities when due, not including any possible additional terms for patent term adjustments or patent term extensions. We do not know if any patent will issue from any of these applications and, if any issue, we do not know whether the issued patents will provide significant proprietary protection or commercial advantage against our competitors or generics. Even if they are issued, our patents may be circumvented, challenged, opposed and found to be invalid or unenforceable.

We filed a composition of matter patent application covering MRG-201 in September 2015 in the United States as U.S. 14/848,085 and a PCT application PCT/US2015/49018 to access foreign countries. The U.S. patent application issued as U.S. 9,376,681 on June 28, 2016, which will expire in September of 2035 if we continue to pay the maintenance fees and annuities when due, with the possibility of Patent Term Extension that may be granted by the USPTO due to administrative delays in the FDA. Prior to the issue of this application, we filed a continuation application in June 2016 also directed to compositions of matter in the United States, as U.S. 15/175,636, and this application is currently pending. We also have issued patents and pending applications that cover various therapeutic uses and generic compositions comprising MRG-201. Collectively, these patents and patent applications, if they issue, would have patent expirations ranging from 2028 to 2035 if we continue to pay the maintenance fees and annuities when due, not including any possible additional terms for patent term adjustments or patent term extensions. We do not know if any patent will issue from any of the pending applications and, if any issue, we do not know whether the issued patents will provide significant proprietary protection or commercial advantage against our competitors or generics. Even if they are issued, our patents may be circumvented, challenged, opposed and found to be invalid or unenforceable.

For our earlier stage product candidates, we have filed compositions of matter and methods of use patent applications in the United States, under the Patent Cooperation Treaty, or the PCT.

In addition to patent protection, we seek to rely on trade secret protection, trademark protection and know-how to expand our proprietary position around our chemistry, technology and other discoveries and inventions that we consider important to our business. We also seek to protect our intellectual property in part by entering into confidentiality agreements with our employees, consultants, scientific advisors, clinical investigators and other contractors and also by requiring our employees, commercial contractors, and certain consultants and investigators, to enter into invention assignment agreements that grant us ownership of any discoveries or inventions made by them. Further, we seek trademark protection in the United States and internationally where available and when we deem appropriate. We have obtained registrations for the Miragen trademark, which we use in connection with our

pharmaceutical research and development services as well as our clinical-stage product candidates. We currently have such registrations for Miragen in the United States, Canada, Japan and the European Union.

Competition

The biotechnology and pharmaceutical industries are characterized by intense and rapidly changing competition to develop new technologies and proprietary products. Our clinical and pre-clinical product candidates may address multiple markets. Ultimately, the diseases our product candidates target for which we may receive marketing authorization will determine our competition. We believe that for most or all of our product development programs, there will be one or more competing programs under development by other companies. Any products that we may commercialize will have to compete with existing therapies and new therapies that may become available in the future. We face potential competition from many different sources, including larger and better-funded biotechnology and pharmaceutical companies. In many cases, the companies with competing programs will have access to greater resources and expertise than we do and may be more advanced in those programs.

We believe that our current and future competition for resources and eventually for customers can be grouped into three broad categories:

- companies working to develop microRNA targeted products, including Regulus Therapeutics Inc., Mirna Therapeutics, Inc., Microlin Bio, Inc., and InteRNA Technologies B.V.;
- companies working to develop other types of oligonucleotide therapeutic products, including Ionis Pharmaceuticals, Inc., Alnylam Pharmaceuticals, Inc., Arrowhead Pharmaceuticals, Inc., Dicerna Pharmaceuticals, Inc., RaNa Therapeutics, Inc., RXi Pharmaceuticals Corporation, and Silence Therapeutics AG; and
- companies with marketed products and development programs for therapeutics that treat the same diseases for which we may also be developing potential treatments.

- The following companies have therapeutics marketed or in development for CTCL: Actelion Ltd, Bristol-Myers Squibb Company, Celgene Corporation, Merck & Co., Inc., Mylan Pharmaceuticals Inc., Novartis International AG, Spectrum Pharmaceuticals, Inc., Seattle Genetics, Inc., Takeda Pharmaceutical Company Ltd, and Valeant Pharmaceuticals International, Inc.

- The following companies have marketed therapeutics for pulmonary fibrosis: Boehringer Ingelheim GmbH, F. Hoffmann-La Roche Ltd.

We believe that the key competitive factors that will affect the success of any of our product candidates, if commercialized, are likely to be their efficacy, safety, convenience, price and the availability of reimbursement from government and other third-party payors relative to such competing products. Our commercial opportunity could be reduced or eliminated if our competitors have products that are superior in one or more of these categories.

Government Regulation

FDA Drug Approval Process

In the United States, pharmaceutical products are subject to extensive regulation by the U.S. Food and Drug Administration, or the FDA. The Federal Food, Drug, and Cosmetic Act, and other federal and state statutes and regulations, govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling and import and export of pharmaceutical products. Failure to comply with applicable U.S. requirements at any time during the product development process may subject a company to a variety of administrative or judicial sanctions, such as imposition of clinical hold, FDA refusal to approve pending new drug applications, or NDAs, warning or untitled letters, withdrawal of approval, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties and criminal prosecution.

We cannot market a drug product candidate in the United States until the drug has received FDA approval. The steps required before a drug may be marketed in the United States generally include the following:

- completion of extensive pre-clinical laboratory tests, animal studies, and formulation studies in accordance with the FDA's good laboratory practices, or GLP, regulations;

- submission to the FDA of an investigational new drug application, or IND, for human clinical testing, 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 at that site;

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

- submission to the FDA of an NDA after completion of all pivotal clinical trials;

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

- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities at which the active pharmaceutical ingredient, or API, and finished drug product are produced and tested to assess compliance with current good manufacturing practices, or cGMPs; and

- FDA review and approval of the NDA prior to any commercial marketing or sale of the drug in the United States.

Satisfaction of FDA pre-market approval requirements typically takes many years and the actual time required may vary substantially based upon the type, complexity and novelty of the product or disease.

Pre-clinical tests include laboratory evaluation of product chemistry, formulation and toxicity, as well as animal trials to assess the characteristics and potential safety and efficacy of the product. The conduct of the pre-clinical tests must comply with federal regulations and requirements, including GLP. An IND sponsor must submit the results of pre-clinical testing to the FDA as part of an IND along with other information, including information about product chemistry, manufacturing and controls and a proposed clinical trial protocol. Long term pre-clinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue after the IND is submitted.

A 30-day waiting period after the submission of each IND is required prior to the commencement of clinical testing in humans. If the FDA has neither commented on nor questioned the IND within this 30-day period, the clinical trial proposed in the IND may begin if all other requirements, including IRB review and approval, have been met. If the FDA raises concerns or questions about the conduct of the trial, such as whether human research subjects will be exposed to an unreasonable health risk, the IND sponsor and the FDA must resolve any outstanding FDA concerns or questions before clinical trials can proceed.

Clinical trials involve the administration of the investigational new drug to healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted in compliance with federal regulations, including GCP requirements, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Clinical trials are conducted under protocols detailing the

objectives of the trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. Each protocol and subsequent protocol amendments must be submitted to the FDA as part of the IND.

The FDA may order the temporary, or permanent, discontinuation of a clinical trial at any time, or impose other sanctions, if it believes that the clinical trial either is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial patients. The study protocol and informed consent information for patients in clinical trials must also be submitted to an IRB, for approval at each site at which the clinical trial will be conducted. 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. Information about certain clinical trials must be submitted within specific timeframes to the NIH, for public dissemination on their *www.clinicaltrials.gov* website.

Clinical trials to support NDAs for marketing approval are typically conducted in three sequential phases, but the phases may overlap. In Phase 1, the initial introduction of the drug into healthy human subjects or patients, the drug is tested to assess pharmacological actions, side effects associated with increasing doses and, if possible, early evidence of effectiveness. Phase 2 usually involves trials in a limited patient population to study metabolism of the drug, pharmacokinetics, the effectiveness of the drug for a particular indication, dosage tolerance and optimum dosage, and to identify common adverse effects and safety risks. If a compound demonstrates evidence of effectiveness and an acceptable safety profile in Phase 2 evaluations, Phase 3 clinical trials, also called pivotal trials, are undertaken to obtain the additional information about clinical efficacy and safety in a larger number of patients, typically at geographically dispersed clinical trial sites, to permit the FDA to evaluate the overall benefit-risk relationship of the drug and to provide adequate information for the labeling of the drug. In most cases the FDA requires two adequate and well controlled Phase 3 clinical trials to demonstrate the efficacy of the drug. A single Phase 3 clinical trial with other confirmatory evidence may be sufficient in rare instances where the study is a large multicenter trial demonstrating internal consistency and a statistically very persuasive finding of a clinically meaningful effect on mortality, irreversible morbidity or prevention of a disease with a potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible.

After completion of the required clinical testing, an NDA is prepared and submitted to the FDA. FDA approval of the NDA is required before marketing of the product may begin in the United States. The NDA must include the results of all pre-clinical, clinical and other testing and a compilation of data relating to the product's pharmacology, chemistry, manufacture and controls. The cost of preparing and submitting an NDA is substantial. The submission of most NDAs is additionally subject to a substantial application user fee, and the manufacturer and/or sponsor under an approved NDA are also subject to annual product and establishment user fees. These fees are typically increased annually. Under the Prescription Drug User Fee Act, or PDUFA, guidelines that are currently in effect, the FDA has a goal of ten months from the date of "filing" of a standard NDA for a new molecular entity to review and act on the submission. This review typically takes twelve months from the date the NDA is submitted to FDA because the FDA has 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. Once the submission is accepted for filing, the FDA begins an in-depth review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. The FDA reviews an NDA to determine, among other things, whether the drug is safe and effective and whether the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product's continued safety, quality and purity.

The FDA may also refer applications for novel drug products, or drug 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 recommendation of an advisory committee, but it generally follows such recommendations. Before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCPs. Additionally, the FDA will inspect the facility or the facilities at which the drug is manufactured. The FDA will not approve the product unless compliance with cGMPs, is satisfactory and the NDA contains data that provide substantial evidence that the drug is safe and effective in the indication studied.

After the FDA evaluates the NDA and the manufacturing facilities, it issues either an approval letter or a complete response letter. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing, or information, in order for the FDA to reconsider the application. If, or 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.

An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, 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 and use restrictions or other risk management mechanisms under a Risk Evaluation and Mitigation Strategy, or REMS, to ensure that the benefits of the drug outweigh the potential risks.

A REMS can include a medication guide, a communication plan for healthcare professionals and elements to assure safe use, such as special training and certification requirements for individuals who prescribe or dispense the drug, requirements that patients enroll in a registry and other measures that the FDA deems necessary to assure the safe use of the drug. The requirement for a REMS can materially affect the potential market and profitability of the drug. The FDA may prevent or limit further marketing of a product based on the results of post-marketing studies or surveillance programs. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

Changes to some of the conditions established in an approved application, including changes in indications, labeling, or manufacturing processes or facilities, require submission and FDA approval of a new NDA or NDA supplement before the change can be implemented. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing NDA supplements as it does in reviewing NDAs. Such supplements are typically reviewed within 10 months of receipt.

Expedited Development and Review Programs

The FDA has a Fast Track program that is intended to expedite or facilitate the process for development and review of new drug products that meet certain criteria. Specifically, new drug products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening disease or condition and demonstrate the potential to address unmet medical needs for the disease or condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug may request that the FDA designate the drug as a Fast Track product at any time during the clinical development of the product. For a Fast Track-designated product, the FDA may consider for review sections of the marketing application on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the application, the FDA agrees to accept sections of the application and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the application.

Any product submitted to the FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. Any product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug product designated for priority review in an effort to facilitate the review. Additionally, a product may be eligible for accelerated approval. Drug products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may be eligible for accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require that a sponsor of a drug

product subject to accelerated approval perform adequate and well-controlled post-marketing clinical trials. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product.

In addition, under the provisions of the Food and Drug Administration Safety and Innovation Act, or FDASIA, the FDA established the Breakthrough Therapy Designation which is intended to expedite the development and review of products that treat serious or life-threatening diseases or conditions. A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The designation includes all of the features of Fast Track designation, as well as more intensive FDA interaction and guidance. The Breakthrough Therapy Designation is distinct from both accelerated approval and priority review, but these can also be granted to the same product candidate if the relevant criteria are met. The FDA must take certain actions, such as holding timely meetings and providing advice, intended to expedite the development and review of an application for approval of a breakthrough therapy. Requests for breakthrough therapy designation will be reviewed within 60 days of receipt, and FDA will either grant or deny the request.

Fast Track designation, priority review, accelerated approval and breakthrough therapy designation do not change the standards for approval but may expedite the development or approval process by allowing for approval based on a surrogate endpoint likely to predict clinical benefit of the underlying drug, rather than through a direct measure of clinical benefit. Even if we receive one of these designations for our product candidates, the FDA may later decide that our product candidates no longer meet the conditions for qualification. In addition, these designations may not provide us with a material commercial advantage.

Post-Approval Requirements

Once an NDA is approved, a product may be subject to certain post-approval requirements. For instance, the FDA closely regulates the post-approval marketing and promotion of drugs, including standards and regulations for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and promotional activities involving the internet and social media. Drugs may be marketed only for the approved indications and in accordance with the provisions of the approved labeling.

Adverse event reporting and submission of periodic reports is required following FDA approval of an NDA. The FDA also may require post-marketing testing, known as Phase 4 testing, REMS, surveillance to monitor the effects of an approved product, or restrictions on the distribution or use of the product. In addition, quality-control, drug manufacture, packaging and labeling procedures must continue to conform to cGMPs after approval. Drug manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies. Registration with the FDA subjects entities to periodic unannounced inspections by the FDA, during which the agency inspects manufacturing facilities to assess compliance with cGMPs. Accordingly, manufacturers must continue to expend time, money and effort in the areas of production and quality-control to maintain compliance with cGMPs. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or failure to comply with regulatory requirements, may result in mandatory 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 REMS 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, 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 approvals;
- product seizure or detention, or refusal to permit the import or export of products; or injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs 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.

Foreign Regulation

In order to market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, 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 would need to obtain the necessary approvals by the comparable foreign regulatory authorities before we can commence clinical trials or marketing of the product in foreign countries and jurisdictions.

Some countries outside of the United States have a similar process that requires the submission of a clinical trial application, or CTA, much like the IND prior to the commencement of human clinical trials. In Europe, for example, a CTA must be submitted to each country's national health authority and an independent ethics committee, much like the FDA and IRB, respectively. Once the CTA is approved in accordance with a country's requirements, a clinical trial may proceed in that country. To obtain regulatory approval to commercialize a new drug under European Union regulatory systems, we must submit a marketing authorization application, or MAA. The MAA is similar to the NDA, with the exception of, among other things, country-specific document requirements.

In Canada, biopharmaceutical product candidates are regulated by the Food and Drugs Act and the rules and regulations promulgated thereunder, which are enforced by the Therapeutic Products Directorate of Health Canada, or TPD. Before commencing clinical trials in Canada, an applicant must complete pre-clinical studies and file a CTA with the TPD. After filing a CTA, the applicant must receive different clearance authorizations to proceed with Phase 1 clinical trials, which can then lead to Phase 2 and Phase 3 clinical trials. To obtain regulatory approval to commercialize a new drug in Canada, a new drug submission, or NDS, must be filed with the TPD. If the NDS demonstrates that the product was developed in accordance with the regulatory authorities' rules, regulations and guidelines and demonstrates favorable safety and efficacy and receives a favorable risk/benefit analysis, the TPD issues a notice of compliance which allows the applicant to market the product.

Other Healthcare Laws

Although we currently do not have any products on the market, our current and future business operations may be subject to additional healthcare regulation and enforcement by the federal government and by authorities in the states and foreign jurisdictions in which we conduct our business. Such laws include, without limitation, state and federal anti-kickback, fraud and abuse, false claims, privacy and security, price reporting and physician sunshine laws. Some of our pre-commercial activities are subject to some of these laws.

The federal Anti-Kickback Statute makes it illegal for any person or entity, including a prescription drug manufacturer or a party acting on its behalf to knowingly and willfully, directly or indirectly, solicit, receive, offer, or pay any remuneration that is intended to induce the referral of business, including the purchase, order, lease of any good, facility, item or service for which payment may be made under a federal healthcare program, such as Medicare or Medicaid. The term “remuneration” has been broadly interpreted to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, formulary managers, and beneficiaries on the other. Although there are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution, the exceptions and safe harbors are drawn narrowly. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all its facts and circumstances. Several courts have interpreted the statute’s intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the Anti-Kickback Statute has been violated. In addition, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. Violations of this law are punishable by up to five years in prison, and can also result in criminal fines, civil money penalties and exclusion from participation in federal healthcare programs.

Moreover, a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act.

The federal civil False Claims Act prohibits, among other things, any person or entity from knowingly presenting, or causing to be presented, for payment to, or approval by, federal programs, including Medicare and Medicaid, claims for items or services, including drugs, that are false or fraudulent or not provided as claimed. Persons and entities can be held liable under these laws if they are deemed to “cause” the submission of false or fraudulent claims by, for example, providing inaccurate billing or coding information to customers or promoting a product off-label. In addition, our future activities relating to the reporting of wholesaler or estimated retail prices for our products, the reporting of prices used to calculate Medicaid rebate information and other information affecting federal, state and third-party reimbursement for our products, and the sale and marketing of our products, are subject to scrutiny under this law. Penalties for federal civil False Claims Act violations may include up to three times the actual damages

sustained by the government, plus mandatory civil penalties of between $10,781.40 and $21,652.80 for each separate false claim, the potential for exclusion from participation in federal healthcare programs, and, although the federal False Claims Act is a civil statute, False Claims Act violations may also implicate various federal criminal statutes.

The Health Insurance Portability and Accountability Act of 1996, or HIPAA, created additional federal criminal statutes that prohibit, among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payors, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense, and knowingly and willfully falsifying, concealing or covering up a material