Use these links to rapidly review the document
TABLE OF CONTENTS
TABLE OF CONTENTS

Table of Contents

Filed Pursuant to Rule 424(b)(5)
Registration No. 333-225434

The information in this preliminary prospectus supplement is not complete and may be changed. A registration statement relating to these securities has become effective by rule of the Securities and Exchange Commission. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities, and we are not soliciting offers to buy these securities, in any state or other jurisdiction where the offer or sale is not permitted.

Subject To Completion, Dated June 5, 2018

PRELIMINARY PROSPECTUS SUPPLEMENT
(To Prospectus dated June 5, 2018)

$200,000,000

363,625 Shares Offered by Selling Stockholders

Madrigal Pharmaceuticals

Common Stock
$ Per Share

We are offering up to $200,000,000 of our common stock, and the selling stockholders identified in this prospectus supplement, including certain of our directors and executive officers and affiliates thereof, are offering up to 363,625 shares of our common stock, pursuant to this prospectus supplement and the accompanying prospectus. We will not receive any proceeds from the sale of shares of common stock by the selling stockholders.

Our common stock trades on The Nasdaq Global Market under the trading symbol "MDGL". On June 4, 2018, the last reported sale price of our common stock on The Nasdaq Global Market was $273.24 per share.

Investing in our common stock involves a high degree of risk. You should carefully consider the risks described under the heading "Risk Factors" beginning on page S-10 of this prospectus supplement before buying shares of our common stock.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus supplement or the accompanying prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

	Per Share	Total
Public offering price	$	$
Underwriting discounts and commissions	$	$
Proceeds, before expenses, to us	$	$
Proceeds, before expenses, to the selling stockholders	$	$

We have agreed to reimburse the underwriter for certain expenses in connection with this offering. See "Underwriting".

The underwriter has the option to purchase up to an aggregate amount of 15% of the base deal shares from us at the public offering price, less the underwriting discounts and commissions payable by us, within 30 days from the date of this prospectus supplement. If the underwriter exercises the option in full, the total underwriting discounts and commissions payable by us will be $, and the total proceeds to us, before expenses, will be $.

The underwriter expects to deliver the shares against payment in New York, New York on or about June , 2018.

Goldman Sachs & Co. LLC

The date of this prospectus supplement is June , 2018

TABLE OF CONTENTS

ABOUT THIS PROSPECTUS SUPPLEMENT

This document is part of a registration statement that we filed with the Securities and Exchange Commission, or the SEC, using a "shelf" registration process and consists of two parts. The first part is the prospectus supplement, including the documents incorporated by reference herein, which describes the specific terms of this offering. The second part, the accompanying prospectus, including the documents incorporated by reference therein, provides more general information. In general, when we refer only to the prospectus, we are referring to both parts of this document combined. Before you invest, you should carefully read this prospectus supplement, the accompanying prospectus, all information incorporated by reference herein and therein, as well as the additional information described under the heading "Where You Can Find More Information." These documents contain information you should carefully consider when deciding whether to invest in our common stock.

This prospectus supplement may add, update or change information contained in the accompanying prospectus. To the extent there is a conflict between the information contained in this prospectus supplement and the accompanying prospectus, you should rely on information contained in this prospectus supplement, provided that if any statement in, or incorporated by reference into, one of these documents is inconsistent with a statement in another document having a later date, the statement in the document having the later date modifies or supersedes the earlier statement. Any statement so modified will be deemed to constitute a part of this prospectus only as so modified, and any statement so superseded will be deemed not to constitute a part of this prospectus.

You should rely only on the information contained in this prospectus supplement, the accompanying prospectus, any document incorporated by reference herein or therein, or any free writing prospectuses we may provide to you in connection with this offering. Neither we nor any of the sales agents or the selling stockholders have authorized anyone to provide you with any different information. We and the selling stockholders take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may provide to you. The information contained in this prospectus supplement, the accompanying prospectus, and in the documents incorporated by reference herein or therein is accurate only as of the date such information is presented. Our business, financial condition, results of operations and prospects may have changed since that date.

This prospectus supplement and the accompanying prospectus do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the shares of common stock to which it relates, nor do this prospectus supplement and the accompanying prospectus constitute an offer to sell or the solicitation of an offer to buy securities in any jurisdiction to any person to whom it is unlawful to make such offer or solicitation in such jurisdiction.

Unless otherwise indicated, information contained in or incorporated by reference into this prospectus concerning our industry and the markets in which we operate, including market opportunity, market position and competitive landscape, is based on information from our management's estimates, as well as from industry publications, surveys and studies conducted by third parties. Management estimates are derived from publicly available information, our knowledge of our industry, and assumptions based on such information and knowledge, which we believe to be reasonable. In addition, while we believe that information contained in the industry publications, surveys and studies has been obtained from reliable sources, the accuracy and completeness of such information is not guaranteed, and we have not independently verified any of the data contained in these third-party sources.

This prospectus supplement and the accompanying prospectus, and any documents incorporated by reference herein or therein, include statements that are based on various

assumptions and estimates that are subject to numerous known and unknown risks and uncertainties. Some of these risks and uncertainties are described under the heading "Risk Factors" beginning on page S-10 of this prospectus supplement and in the section titled "Risk Factors" in our most recent Annual Report on Form 10-K, and our Quarterly Report on Form 10-Q for the quarter ended March 30, 2018, which are incorporated by reference into the prospectus. These and other important factors could cause our future results to be materially different from the results expected as a result of, or implied by, these assumptions and estimates. You should read the information contained in this prospectus supplement and the accompanying prospectus, and the documents incorporated by reference herein and therein, completely and with the understanding that future results may be materially different and worse from what we expect. See the information included under the heading "Special Note Regarding Forward-Looking Statements."

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

Unless otherwise indicated or the context otherwise requires, the terms "Company," "Madrigal Pharmaceuticals," "we," "us" and "our" refer to Madrigal Pharmaceuticals, Inc., a Delaware corporation, and its predecessors and consolidated subsidiaries.

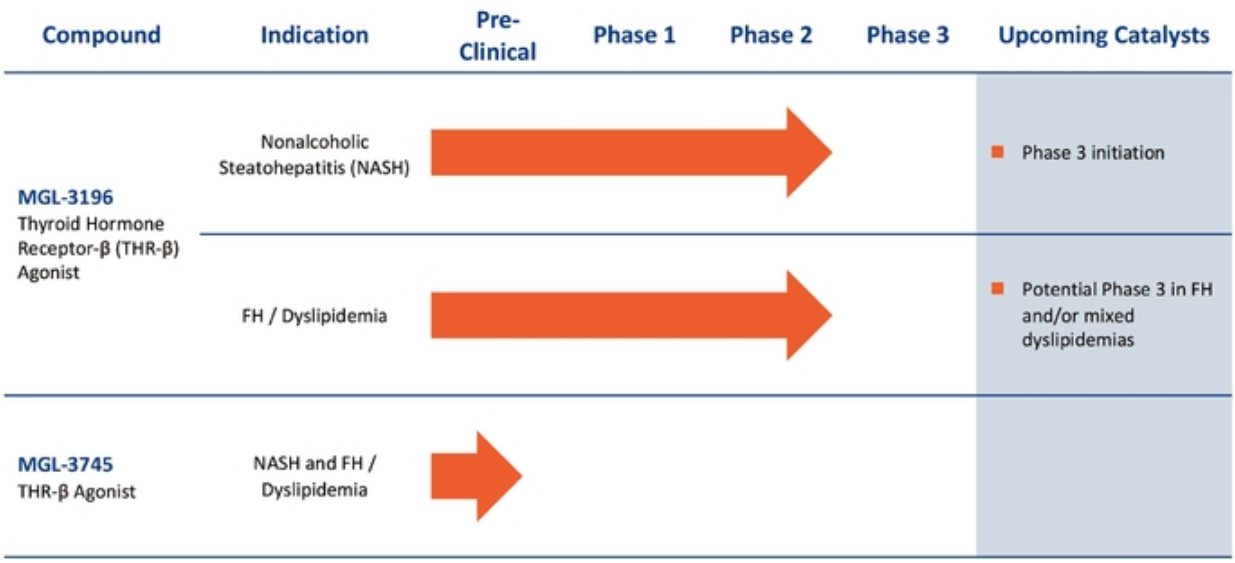
PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights information contained elsewhere in this prospectus supplement and the accompanying prospectus and in the documents we incorporate by reference. This summary does not contain all of the information that you should consider before deciding to invest in our common stock. You should read this entire prospectus supplement and the accompanying prospectus carefully, including the "Risk Factors" section contained in this prospectus supplement and our consolidated financial statements and the related notes and the other documents incorporated by reference herein.

Overview

We are a clinical-stage biopharmaceutical company focused on the development and commercialization of innovative therapeutic candidates for the treatment of cardiovascular, metabolic, and liver diseases. Our lead product candidate, MGL-3196, is a proprietary, liver-directed, selective thyroid hormone receptor-ß, or THR-ß, agonist being developed as a once-daily oral pill that can potentially be used to treat a number of disease states with high unmet medical need, including non-alcoholic steatohepatitis, or NASH. For NASH, we enrolled 125 patients in a Phase 2 clinical trial. We achieved the 12-week primary endpoint for this Phase 2 clinical trial and reported the results in December 2017, and we reported positive topline 36-week results at the conclusion of the Phase 2 clinical trial in May 2018. We are also developing MGL-3196 for dyslipidemia, including genetic dyslipidemias such as heterozygous familial hypercholesterolemia, or HeFH. We enrolled 116 patients and completed a Phase 2 clinical trial in HeFH patients, and we reported the results in February 2018. In addition to the NASH and HeFH Phase 2 clinical trials, MGL-3196 has also been studied in six completed Phase 1 trials in a total of 183 subjects. MGL-3196 appeared to be safe and was well-tolerated in these trials, which included a single ascending dose trial, a multiple ascending dose trial, two drug interaction trials with statins, a multiple dose mass balance study, and a single dose relative bioavailability study of tablet formulations versus capsule formulation.

The following chart summarizes the status of our product candidate development programs for MGL-3196 and MGL-3745, a preclinical compound, which has similar thyroid receptor selectivity to MGL-3196 and is thus a potential backup compound for MGL-3196:



Recent Developments

In May 2018, we announced positive top-line 36-week results from our Phase 2 clinical trial in NASH. In this clinical trial, MGL-3196 demonstrated statistical significance in the primary endpoint (p<0.0001), the relative reduction of liver fat on magnetic resonance imaging-estimated proton density fat fraction, or MRI-PDFF, at 12-weeks in December 2017, and, as we reported in May 2018, statistically significant results in multiple 36-week endpoints, including key secondary endpoints, reduction and resolution of NASH on liver biopsy as set forth in the table below.

	MGL-3196	MGL-3196 MRI-PDFF Responders[1]	Placebo
Number of patients with baseline and end-of-study liver biopsies[2]	73	46	34
> **2 Point Decrease in NAS**	56% p=0.02	70% p=0.001	32%
NASH Resolution	27% p=0.02	39% p=0.001	6%

(1) MGL-3196 MRI-PDFF Responders = MGL-3196 treated patients with >=30% relative fat reduction on Week 12 MRI-PDFF

(2) does not include one end-of-study liver biopsy that was inadequate

MGL-3196 treated patients with greater than or equal to 30% fat reduction on MRI-PDFF at 12-weeks demonstrated a higher percentage of nonalcoholic fatty liver disease activity score, or NAS, reduction and NASH resolution. In patients with NASH resolution, 35% of MGL-3196 treated patients and no placebo patients had a baseline NAS greater than or equal to five. In MGL-3196 patients with NASH resolution, fibrosis also resolved in 50% of such patients and was decreased statistically significantly relative to all placebo patients.

Further, 36-week results from our Phase 2 clinical trial in NASH showed:

- Sustained, highly statistically significant (p<0.0001) reduction in liver fat compared with placebo on 36-week MRI-PDFF and mean relative fat reduction of 37% with MGL-3196 treated patients in contrast with 8.9% with placebo patients;
- Sustained, statistically significant reductions in low-density lipoprotein cholesterol, or LDL-C, apolipoprotein B (ApoB), triglycerides, and lipoprotein(a) (Lp(a));
- Statistically significant reductions in liver enzymes, of greater magnitude with longer duration of MGL-3196 treatment;
- Statistically significantly more MGL-3196 treated patients than placebo patients had normalization of alanine aminotransferase;
- Statistically significant reductions in fibrosis biomarkers in MGL-3196 treated patients as compared with placebo patients;
- On liver biopsy, fibrosis was reduced by at least one point in 23% of placebo patients and 29% of MGL-3196 treated patients;
- Very good all subject tolerability: mostly mild and a few moderate adverse events, or AEs, which were balanced between drug treated patients and placebo patients; and
- An increase in incidence of a transient mild diarrhea at beginning of study, often a single episode, in MGL-3196 treated patients compared with placebo patients.

Our Strategy

Our goal is to become a leading biopharmaceutical company developing and potentially commercializing innovative liver-directed, ß-selective thyroid hormone receptor agonists for the treatment of cardiometabolic and liver disease. To achieve our goal, we plan to:

- **Complete clinical development and seek regulatory approval of MGL-3196 in NASH.** We have reported data for the primary endpoint and multiple secondary endpoints from our Phase 2 study in NASH in each of December 2017 and May 2018. NASH is a disease driven by the growing epidemic of obesity, with a significant unmet need for approved therapies that are effective and well tolerated. We believe MGL-3196 is an excellent candidate for the chronic treatment of NASH because of its pleiotrophic actions on the liver, including, importantly decreasing lipotoxicity, thereby potentially resolving NASH and reducing liver fibrosis, and its safety profile based on the results to date.

- **Establish commercial capabilities to market MGL-3196 as a leading treatment for NASH.** If approved, we may choose either to establish a sales and marketing organization with technical expertise and supporting distribution capabilities to commercialize MGL-3196, or to collaborate with one or more third parties to accomplish these tasks. Patients with NASH are primarily managed by a concentrated group of liver specialists in the United States and Europe. We believe this will enable us to launch MGL-3196 in NASH in a cost-effective, targeted manner.

- **Grow our pipeline through additional indications for MGL-3196 including orphan indications.** We believe that MGL-3196 has the potential to be an effective treatment for other disease indications such as dyslipidemias including heterozygous familial hypercholesterolemia, or HeFH, and the much rarer homozygous state, homozygons familial hypercholesterolemia or HoFH. We plan to pursue orphan drug designation where possible.

Market Opportunity in NASH

NASH is a serious inflammatory form of nonalcoholic fatty liver disease, or NAFLD. NAFLD has become the most common liver disease in the United States and other developed countries and is characterized by an accumulation of fat in the liver with no other apparent causes. The rising worldwide prevalence of obesity-related disorders has contributed to a rapid increase in the global prevalence of NASH and NAFLD. In the United States, NAFLD is estimated to affect approximately 27% to 34% of the population, or an estimated 86 million to 108 million people, and approximately 10% to 20% of those will progress from NAFLD to NASH. Current estimates place NASH prevalence at approximately 9 million to 15 million people in the United States, or 3% to 5% of the population, with similar prevalence in Europe and Asia. The prevalence of NASH is also increasing in developing regions due to the adoption of a more sedentary lifestyle and a diet consisting of processed foods with high fat and fructose content.

The Centers for Disease Control and Prevention projects the prevalence of obesity to increase from 34% of the United States population to 42% of the United States population by 2030. Driven by this epidemic of obesity, NASH is projected to become the leading cause of liver transplants by 2020. Given the extremely limited availability of organ donors and high transplant costs, NASH patients who require transplantation will place a significant economic burden on the healthcare system. As such, there is a significant unmet medical need for well-tolerated oral treatments for NASH. Because there are currently no therapeutic products approved for the treatment of NASH, the market size is difficult to estimate. However, based on our analysis of multiple market assessments, we estimate that the addressable NASH population is several million patients worldwide, and that NASH could become a multi-billion dollar market able to support multiple approved drug products.

General Information

We were incorporated in Delaware in September 2011. Our principal executive offices are located at 200 Barr Harbor Drive, Suite 400, West Conshohocken, Pennsylvania 19428. Our telephone number is (484) 380-9263. Our Internet website address is www.madrigalpharma.com. The contents of our website are not incorporated into, and do not form a part of, this prospectus supplement or the registration statement of which it forms a part.

The Offering

The following summary contains basic information about our common stock and the offering and is not intended to be complete. It does not contain all of the information that may be important to you. For a more complete understanding of our common stock, you should read the section entitled "Description of Capital Stock."

Common stock offered by us	$200,000,000 of shares of our common stock.
Common stock offered by our selling stockholders	363,625 shares.
Common stock to be outstanding after this offering[(1)]	14,990,640 shares, plus any shares the underwriter may purchase from the Company by exercising its option to purchase additional shares (see below).
Option to purchase additional shares	The underwriter has been granted an option to purchase additional shares of our common stock from us up to an aggregate amount of 15% of the base deal shares. This option is exercisable, in whole or in part, for a period of 30 days following the date of this prospectus supplement.
Use of Proceeds	We estimate that the net proceeds from this offering to us will be approximately $188.5 million based on the assumed sale of $200,000,000 of shares of our common stock offered hereby (or approximately $230.8 million if the underwriter exercises its option to purchase an assumed $44,900,000 of additional shares from us in full), after deducting estimated underwriting discounts and commissions and estimated offering expenses. We intend to use the net proceeds from this offering, if any, for general corporate purposes, including, without limitation, research and development expenditures, clinical trial expenditures, manufacture and supply of drug substance and drug products, acquisitions of new technologies, capital expenditures and working capital. See "Use of Proceeds" beginning on page S-39 of this prospectus supplement. We will not receive any proceeds from the sale of shares of common stock by the selling stockholders.
Nasdaq Global Market Symbol	MDGL

Risk Factors	Your investment in our common stock involves substantial risks. You should read carefully the "Risk Factors" included and incorporated by reference in this prospectus supplement and the accompanying prospectus, including the risk factors incorporated by reference from our filings with the SEC.

(1) The common stock outstanding after the offering is based on 14,250,726 shares of our common stock outstanding as of May 31, 2018 and excludes the following:

- 1,969,797 shares of common stock issuable upon conversion of our Series A Convertible Preferred Stock outstanding as of March 31, 2018;
- 1,122,585 shares of our common stock issuable upon the exercise of options outstanding as of March 31, 2018, having a weighted average exercise price of $28.63 per share; and
- an aggregate of 1,289,595 shares of our common stock reserved for future issuance as of March 31, 2018 under our 2015 Stock Plan.

Except as otherwise noted, all information in this prospectus supplement assumes no exercise by the underwriter of its option to purchase additional shares of our common stock.

RISK FACTORS

Before making an investment decision, you should carefully consider the risks described below and discussed in the section titled "Risk Factors" in our most recent Annual Report on Form 10-K, as well as the risks, uncertainties and additional information set forth in our SEC reports on Forms 10-K, 10-Q and 8-K and in other documents incorporated by reference in this prospectus supplement and the accompanying prospectus. We expect to update these Risk Factors from time to time in the periodic and current reports that we file with the SEC after the date of this prospectus supplement. These updated Risk Factors will be incorporated by reference in this prospectus supplement.

Our business, financial condition or results of operations could be materially adversely affected by any of these risks. The trading price of our common stock could decline due to any of these risks, and you may lose all or part of your investment. The risks and uncertainties we have described are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our business, financial condition results of operations and prospects. Certain statements below are forward-looking statements. See the information included under the heading "Special Note Regarding Forward-Looking Statements."

Risks Related to Our Business

We have limited operating history, we have incurred significant operating losses since inception and we expect to incur significant operating losses for the foreseeable future. We may never become profitable or, if achieved, be able to sustain profitability.

We have incurred significant operating losses since our inception and expect to incur significant losses for the foreseeable future as we continue our clinical trial and development programs for MGL-3196 and other future product candidates. As of March 31, 2018, we had an accumulated deficit of approximately $112.8 million. Losses have principally resulted from costs incurred in our preclinical and clinical trials, research and development programs and from our general and administrative expenses. As of March 31, 2018, we had cash, cash equivalents and marketable securities of approximately $182.8 million. In the future, we intend to continue to conduct research and development, clinical testing, regulatory compliance and, if MGL-3196 or other future product candidates are approved, sales and marketing activities that, together with anticipated general and administrative expenses, will likely result in us incurring further significant losses for the foreseeable future.

We currently generate no revenue from product sales, and we may never be able to commercialize MGL-3196 or other future product candidates. We do not currently have the required approvals to market MGL-3196 or any other future product candidates, and we may never receive them. We may not be profitable even if we or any of our future development partners succeed in commercializing any of our product candidates. Because of the numerous risks and uncertainties associated with developing and commercializing our product candidates, we are unable to predict the extent of any future losses or when we will become profitable, if at all.

Our business depends on the success of MGL-3196, which is still in clinical development and has not completed a pivotal trial. If we are unable to obtain regulatory approval for and successfully commercialize MGL-3196, or we experience significant delays in doing so, our business will be materially harmed.

To date, the sole focus of our product development has been MGL-3196, a liver-directed selective thyroid hormone receptor beta agonist for potential use in non-alcoholic steatohepatitis, or NASH, and familial hypercholesterolemia, or FH. Successful continued development and ultimate regulatory approval of MGL-3196 for NASH or genetic dyslipidemias, such as FH, is critical to the future success of our business. We have invested, and will continue to invest, a significant portion

of our time and financial resources in the clinical development of MGL-3196. We will need to raise sufficient funds to successfully complete our clinical development program for MGL-3196 in NASH and FH. The future regulatory and commercial success of MGL-3196 is subject to a number of risks, including the following:

- we may not have sufficient financial and other resources to complete the necessary clinical trials for MGL-3196, including, but not limited to, our currently ongoing Phase 2 clinical trials and our planned registrational clinical trials to obtain drug approval;
- the mechanism of action of MGL-3196 is complex and we do not know the degree to which it will translate into a therapeutic benefit, if any, in NASH, FH or any other indication, and we do not know the degree to which the complex mechanism of action may contribute to long term safety issues or adverse events, if any, when MGL-3196 is taken for prolonged periods such as in the treatment of NASH, FH or any other indication;
- we may not be able to obtain adequate evidence from clinical trials of efficacy and safety for MGL-3196 in NASH, FH or any other indication;
- we do not know the degree to which MGL-3196 will be accepted as a therapy by physicians, patients and payors, even if approved;
- in our clinical programs for MGL-3196, we may experience variability in patients, adjustments to clinical trial procedures and the need for additional clinical trial sites, which could delay our clinical trial progress;
- the results of our clinical trials may not meet the level of statistical or clinical significance required by the FDA or comparable foreign regulatory bodies for marketing approval;
- patients in our clinical trials may die or suffer other adverse effects for reasons that may or may not be related to MGL-3196, which could delay or prevent further clinical development;
- the standards implemented by clinical or regulatory agencies may change at any time;
- we cannot be certain what efficacy endpoints FDA or foreign clinical or regulatory agencies may require in a Phase 3 clinical trial of NASH or FH or for approval of our product candidates; we also cannot be certain if we will be able to gain accelerated approval of any of our product candidates based on surrogate endpoints;
- the FDA or foreign clinical or regulatory agencies will likely require efficacy endpoints for Phase 3 clinical trials for the treatment of NASH or FH that differ from the endpoints of our current Phase 2 trials and the results of our Phase 3 clinical trials may not be as favorable as the results we have observed to date in our current trials;
- other differences in the design of our planned Phase 3 clinical trials of the treatment of NASH, including the use of a new tablet formulation of MGL-3196 and the inclusion of patients with more advanced NASH, could cause the results of our Phase 3 trials to be less favorable than the results we observed in our Phase 2 trials in NASH;
- if we obtain accelerated approval of a product candidate based on a surrogate endpoint, we will likely be required to conduct a post-approval clinical outcomes trial to confirm the clinical benefit of the product candidate and if the post-approval trial is not successful we may not be able to continue marketing the product;
- we cannot be certain of the number and type of clinical trials and non-clinical studies that FDA or other regulatory agencies will require in order to approve MGL-3196 for NASH or FH;

- if approved for NASH, MGL-3196 will likely compete with the off-label use of currently marketed products and other therapies in development that may reach approval for NASH prior to MGL-3196;
- if approved for FH, MGL-3196 will likely compete with currently approved and marketed products and other therapies in development that may reach approval for FH prior to MGL-3196; and
- we may not be able to obtain, maintain or enforce our patents and other intellectual property rights.

Of the large number of drugs in development in the pharmaceutical industry, only a small percentage results in the submission of a new drug application, or NDA, to the FDA and even fewer are approved for commercialization. Furthermore, even if we do receive regulatory approval to market MGL-3196, any such approval may be subject to limitations on the indicated uses or patient populations for which we may market the products. Accordingly, even if we are able to obtain the requisite financing to continue to fund our development programs, we may be unable to successfully develop or commercialize MGL-3196. If we or any of our future development partners are unable to develop, or obtain regulatory approval for, or, if approved, successfully commercialize MGL-3196, we may not be able to generate sufficient revenue to continue our business.

Clinical trials are very expensive, time-consuming and difficult to design and implement and involve uncertain outcomes. Furthermore, the results of preclinical studies and early clinical trials are not always predictive of future results. Any product candidate that we advance into clinical trials, including MGL-3196, may not have favorable results in later clinical trials or receive regulatory approval.

Drug development has inherent risk. We will be required to demonstrate through adequate and well-controlled clinical trials that our product candidates are safe and effective, with a favorable benefit-risk profile, for use in our target indications before we can seek regulatory approvals for its commercial sale. Clinical studies are expensive, difficult to design and implement, can take many years to complete and are uncertain as to outcome. Delay or failure can occur at any stage of development, including after commencement of any of our clinical trials. In addition, success in early clinical trials does not mean that later clinical trials will be successful, because later-stage clinical trials may be conducted in broader patient populations and involve different study designs. For instance, our Phase 1 results and our Phase 2 primary endpoint results in NASH may not be predictive of any future Phase 2 results or of results in any Phase 3 clinical trial in NASH. Furthermore, our future trials will need to demonstrate sufficient safety and efficacy in significantly larger patient populations for approval by regulatory authorities. Companies frequently suffer significant setbacks in advanced clinical trials, even after earlier clinical trials have shown promising results, and we cannot be certain that we will not face similar setbacks. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products. In addition, only a small percentage of drugs under development result in the submission of an NDA to the FDA and even fewer are approved for commercialization.

We cannot be certain that any of our ongoing or future clinical trials will be successful, and any safety concerns observed in any one of our clinical trials in our targeted indications could limit the prospects for regulatory approval of our product candidates in those and other indications.

Because MGL-3196 has not yet received regulatory approval for any indication, it is difficult to predict the time and cost of development and our ability to successfully complete clinical development and obtain the necessary regulatory approvals for commercialization.

MGL-3196 has not yet received regulatory approval for the treatment of NASH, FH or any other indication, and unexpected problems may arise that could cause us to delay, suspend or terminate our development efforts in any or all indications. Further, MGL-3196 has not yet demonstrated efficacy in patients with NASH or FH, and the long-term safety consequences of a liver-directed thyroid hormone receptor beta agonist are not known. Regulatory approval of new product candidates such as MGL-3196 can be more expensive and take longer than approval for candidates for the treatment of more well-understood diseases with previously approved products.

If clinical trials or regulatory approval processes for our product candidates are prolonged, delayed or suspended, we may be unable to commercialize our product candidates on a timely basis, which would require us to incur additional costs and delay our receipt of any revenue from potential product sales.

We cannot predict whether we will encounter problems with any of our completed, ongoing or planned clinical trials that will cause us or any regulatory authority to delay, suspend, or terminate those clinical trials or delay the analysis of data derived from them. A number of events, including any of the following, could delay or impede completely the completion of our ongoing and planned clinical trials and negatively affect our ability to obtain regulatory approval for, and to market and sell, a particular product candidate:

- conditions imposed on us by the FDA or other regulatory authorities regarding the scope or design of our clinical trials;
- insufficient supply of our product candidates or other materials necessary to conduct and complete our clinical trials;
- slow enrollment and retention rate of subjects in our clinical trials; and
- serious and unexpected drug-related side effects related to the product candidate being tested.

Commercialization of our product candidates may be delayed by the imposition of additional conditions on our clinical trials by the FDA or any other applicable foreign regulatory authority or the requirement of additional supportive studies by the FDA or such foreign regulatory authority.

We do not know whether our clinical trials will begin as planned, will need to be restructured, will enroll an adequate number of patients on time, or will be completed on schedule, if at all. Delays in the initiation, enrollment or completion of our clinical trials will result in increased development costs for our product candidates, and our financial resources may be insufficient to fund any incremental costs. In addition, if our clinical trials are delayed, our competitors may be able to bring products to market before we do and the commercial viability of our product candidates could be limited.

If we inadvertently fail to comply with foreign regulatory requirements governing human clinical trials and marketing approval for drugs, we could be prevented from selling our drug candidates in foreign markets, which may adversely affect our operating results and financial condition.

The requirements governing the conduct of clinical trials, product licensing, pricing, and reimbursement for marketing our drug candidates outside the United States vary greatly from country to country and may require additional testing. We expect that our future clinical

development of our drug candidates will involve a number of clinical trials in foreign jurisdictions, particularly in Europe. We have no experience in obtaining foreign regulatory approvals. The time required to obtain approvals outside the United States may differ from that required to obtain FDA approval. We may not obtain foreign regulatory approvals on a timely basis, if at all. Approval by the FDA does not guarantee approval by regulatory authorities in other countries, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other countries or by the FDA. Failure to comply with these regulatory requirements or obtain required approvals could impair our ability to develop foreign markets for our drug candidates and may have a material adverse effect on our results of operations and financial condition.

We depend on enrollment of patients in our clinical trials for our product candidates. If we encounter difficulties enrolling patients in our clinical trials, our clinical development activities could be delayed or otherwise adversely affected.

Identifying and qualifying patients to participate in clinical trials of our product candidates is critical to our success. We may not be able to initiate, continue, or complete clinical trials required by the FDA or foreign regulatory agencies for MGL-3196 if we are unable to locate and enroll a sufficient number of eligible patients to participate in these clinical trials. We expect our Phase 3 clinical trials of MGL-3196 will require that we enroll significantly more patients than were enrolled in our Phase 2 trials. Patient enrollment, a significant factor in the timing to conduct and complete clinical trials, is affected by many factors, including the size and nature of the patient population, the proximity of patients to clinical sites, the eligibility criteria for the trial, the design of the clinical trial, competing clinical trials, and clinicians' and patients' perceptions as to the potential advantages and disadvantages of the product candidate being studied in relation to other available therapies, including any new drugs that may be approved for the indications we are investigating. For instance, we are aware that other companies conducting clinical trials in NASH patients have had delays in recruiting patients for their trials. In the proposed clinical trials, patient willingness to undergo a liver biopsy in our NASH trials, and identification of patients willing to participate in our FH trials due to the rarity of the disease, are also risk factors. Potential patients for MGL-3196 may not be adequately diagnosed or identified with the diseases which we are targeting or may not meet the entry criteria for our studies.

The FDA typically requires sponsors of lipid-lowering product candidates to conduct drug-drug interaction studies with statins because statins may have increased safety risks when administered together with other drug therapies that affect their pharmacokinetic profile. We have completed two Phase 1 clinical drug interaction studies of MGL-3196 and statins in 39 normal healthy volunteers, which showed MGL-3196 to have a favorable safety profile and to be well-tolerated. We have completed a Phase 2 clinical trial in NASH including patients taking low dose statins. We have also completed a Phase 2 clinical trial in HeFH including patients taking high dose statins. In general, drug interactions between MGL-3196 and statins and any other drug that might result in adverse events could delay development in later clinical trials.

We will be required to identify and enroll a sufficient number of patients for each of our ongoing and planned clinical trials of MGL-3196 for NASH and FH indications, respectively. We also may encounter difficulties in identifying and enrolling NASH patients and FH patients with a stage of disease appropriate for our ongoing or future clinical trials. We may not be able to initiate or continue clinical trials if we are unable to locate a sufficient number of eligible patients to participate in the clinical trials required by the FDA or other foreign regulatory agencies. In addition, the process of finding and diagnosing patients may prove costly. Our inability to enroll a sufficient number of patients for any of our clinical trials would result in significant delays or may require us to abandon one or more clinical trials.

Any product candidate in our current or future clinical trials may cause unacceptable adverse events or side effects or have other properties that may delay or prevent its regulatory approval or commercialization or limit its commercial potential.

Unacceptable adverse events or undesirable side effects caused by any of our product candidates in current or future clinical trials could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in the denial of regulatory approval by the FDA or other regulatory authorities for any or all targeted indications and markets. This in turn could prevent us from completing development of or commercializing the affected product candidate and generating revenue from its sale. If any of our product candidates cause unacceptable adverse events in clinical trials, we may not be able to obtain regulatory approval or commercialize such product candidate.

Occurrence of serious treatment-related side effects could impede subject recruitment and clinical trial enrollment or the ability of enrolled patients to complete the trial, require us to halt the clinical trial, and prevent receipt of regulatory approval from the FDA. They could also adversely affect physician or patient acceptance of our product candidates or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly.

Our product candidates will remain subject to ongoing regulatory review even if they receive marketing approval, and if we fail to comply with continuing regulations, we could lose these approvals and the sale of any approved commercial products could be suspended.

Even if we receive regulatory approval to market a particular product candidate, the manufacturing, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion, sampling, and record keeping related to the product will remain subject to extensive regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMP, regulations and GCPs, for any clinical trials that we conduct post-approval, all of which may result in significant expense and limit our ability to commercialize such products. In addition, any regulatory approvals that we receive for our product candidates may also be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials, and surveillance to monitor the safety and efficacy of the product candidate. The FDA may also require a REMS Program as a condition of approval of our product candidates, which could include requirements for a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools.

If we fail to comply with the regulatory requirements of the FDA and other applicable domestic and foreign regulatory authorities, or previously unknown problems with any approved product, manufacturer, or manufacturing process are discovered, we could be subject to administrative or judicially imposed sanctions, including:

- restrictions on the products, manufacturers, or manufacturing processes;
- warning letters or untitled letters;
- civil or criminal penalties;
- fines;
- injunctions;
- product seizures or detentions;

- pressure to initiate voluntary product recalls;
- suspension or withdrawal of regulatory approvals; and
- refusal to approve pending applications for marketing approval of new products or supplements to approved applications.

If any of these events occurs, our ability to sell such products may be impaired, and we may incur substantial additional expense to comply with regulatory requirements, which could adversely affect our business, financial condition and results of operations.

We operate in a highly competitive and rapidly changing industry, and our product candidates may become obsolete.

We are engaged in a rapidly evolving field. Competition from other pharmaceutical companies, biotechnology companies and research and academic institutions is intense and likely to increase. Many of those companies and institutions have substantially greater financial, technical and human resources than us. Those companies and institutions also have substantially greater experience in developing products, conducting clinical trials, obtaining regulatory approval and in manufacturing and marketing pharmaceutical products. Our competitors may succeed in obtaining regulatory approval for their products more rapidly than we do. Competitors have developed or are in the process of developing technologies that are, or in the future may be, the basis for competitive products. Some of these competitive products may have an entirely different approach or means of accomplishing the desired therapeutic effect than products being developed by us. Our competitors may succeed in developing products that are more effective and/or cost competitive than those we are developing, or that would render our product candidates less competitive or even obsolete. In addition, one or more of our competitors may achieve product commercialization or patent protection earlier than us, which could materially adversely affect our business.

If the FDA or other applicable regulatory authorities approve generic products that compete with any of our or any of our partners' product candidates, the sales of our product candidates would be adversely affected.

Once an NDA or marketing authorization application outside the United States is approved, the product covered thereby becomes a "listed drug" that can, in turn, be cited by potential competitors in support of approval of an abbreviated new drug application in the United States. Agency regulations and other applicable regulations and policies provide incentives to manufacturers to create modified, non-infringing versions of a drug to facilitate the approval of an abbreviated new drug application or other application for generic substitutes in the United States and in nearly every pharmaceutical market around the world. These manufacturers might only be required to conduct a relatively inexpensive study to show that their product has the same active ingredient(s), dosage form, strength, route of administration and conditions of use, or labeling, as our product and that the generic product is bioequivalent to our product, meaning it is absorbed in the body at the same rate and to the same extent as our product. These generic equivalents, which must meet the same quality standards as branded pharmaceuticals, would be significantly less costly than our product to bring to market, and companies that produce generic equivalents are generally able to offer their products at lower prices. Thus, after the introduction of a generic competitor, a significant percentage of the sales of any branded product are typically lost to the generic product. Accordingly, competition from generic equivalents to our product or any of our partners' future products, if any, would materially adversely affect our future revenue, profitability and cash flows and substantially limit our ability to obtain a return on the investments we have made and expect to make in our or any of our partners' product candidates, including MGL-3196.

Competition that our or any of our partners' products may face from generic versions of our products could materially and adversely impact our future revenue, profitability and cash flows and

substantially limit our ability to obtain a return on the investments we have made in those product candidates.

If physicians and patients do not accept our future products or if the market for indications for which any product candidate is approved is smaller than expected, we may be unable to generate significant revenue, if any.

Even if any of our product candidates obtain regulatory approval, they may not gain market acceptance among physicians, patients, and third-party payers. Efforts to educate the medical community and third-party payers on the benefits of our product candidates may require significant resources and may not be successful. If any of our product candidates do not achieve an adequate level of acceptance, we may not generate significant product revenue or any profits from operations. Physicians may decide not to recommend its treatments for a variety of reasons including:

- timing of market introduction of competitive products;
- demonstration of clinical safety and efficacy compared to other products;
- cost-effectiveness;
- limited or no coverage by third-party payers;
- convenience and ease of administration;
- prevalence and severity of adverse side effects;
- restrictions in the label of the drug;
- other potential advantages of alternative treatment methods; and
- ineffective marketing and distribution support of its products.

If any of our product candidates are approved, but fail to achieve market acceptance or such market is smaller than anticipated, we may not be able to generate significant revenue and our business would suffer.

As we evolve from a company that is primarily involved in clinical development to a company that is also involved in commercialization, we may encounter difficulties in expanding our operations successfully.

As we advance our product candidates through clinical trials, we will need to expand our development, regulatory, manufacturing, and marketing and sales capabilities and may need to further contract with third parties to provide these capabilities. As our operations expand, we likely will need to manage additional relationships with such third parties, as well as additional collaborators, distributors, marketers and suppliers.

Maintaining third party relationships for these purposes will impose significant added responsibilities on members of our management and other personnel. We must be able to effectively manage our development efforts; recruit and train sales and marketing personnel, effectively manage our participation in the clinical trials in which our product candidates are involved and improve our managerial, development, operational and finance systems, all of which may impose a strain on our administrative and operational infrastructure.

If we enter into arrangements with third parties to perform sales, marketing or distribution services, any product revenues that we receive, or the profitability of these product revenues to us, are likely to be lower than if we were to market and sell any products that we develop without the involvement of these third parties. In addition, we may not be successful in entering into arrangements with third parties to sell and market our products or in doing so on terms that are

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

The uncertainty associated with pharmaceutical reimbursement and related matters may adversely affect our business.

Market acceptance and sales of any one or more of our product candidates will depend on reimbursement policies and may be affected by future healthcare reform measures in the United States and in foreign jurisdictions. Government authorities and third-party payers, such as private health insurers and health maintenance organizations, decide which drugs they will cover and establish payment levels. We cannot be certain that reimbursement will be available for any of our product candidates. Also, we cannot be certain that reimbursement policies will not reduce the demand for, or the price paid for, our products. If reimbursement is not available or is available on a limited basis, we may not be able to successfully commercialize any product candidates that we develop.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, also called the Medicare Modernization Act, or MMA, changed the way Medicare covers and pays for pharmaceutical products. The legislation established Medicare Part D, which expanded Medicare coverage for outpatient prescription drug purchases by the elderly but provided authority for limiting the number of drugs that will be covered in any therapeutic class. The MMA also introduced a new reimbursement methodology based on average sales prices for physician-administered drugs. The United States and several foreign jurisdictions are considering, or have already enacted, a number of legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our products profitably. Among policy makers and payers in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access to healthcare. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives. We expect to experience pricing pressures in connection with the sale of any products that we develop due to the trend toward managed healthcare, the increasing influence of health maintenance organizations, and additional legislative proposals.

In March 2010, the Patient Protection and Affordable Care Act, or ACA, became law in the United States. The goal of ACA is to reduce the cost of healthcare and substantially change the way healthcare is financed by both government and private insurers. While we cannot predict what impact on federal reimbursement policies this legislation will have in general or on our business specifically, the ACA may result in downward pressure on pharmaceutical reimbursement, which could negatively affect market acceptance of, and the price we may charge for, any products we develop that receives regulatory approval. We also cannot predict the impact of ACA on us as many of the ACA reforms require the promulgation of detailed regulations implementing the statutory provisions, which have not yet been fully implemented.

If any product liability lawsuits are successfully brought against us or any of our collaborative partners, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.

We face an inherent risk of product liability lawsuits related to the testing of our product candidates in seriously ill patients and will face an even greater risk if product candidates are approved by regulatory authorities and introduced commercially. Product liability claims may be brought against us or our partners by participants enrolled in our clinical trials, patients, healthcare

providers or others using, administering or selling any of our future approved products. If we cannot successfully defend ourselves against any such claims, we may incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any of our future approved products;
- injury to our reputation;
- withdrawal of clinical trial participants;
- termination of clinical trial sites or entire trial programs;
- significant litigation costs;
- substantial monetary awards to or costly settlements with patients or other claimants;
- product recalls or a change in the indications for which products may be used;
- loss of revenue;
- diversion of management and scientific resources from our business operations; and
- the inability to commercialize our product candidates.

If any of our product candidates are approved for commercial sale, we will be highly dependent upon consumer perceptions of us and the safety and quality of our products. We could be adversely affected if we are subject to negative publicity. We could also be adversely affected if any of our products or any similar products distributed by other companies prove to be, or are asserted to be, harmful to patients. Also, because of our dependence upon consumer perceptions, any adverse publicity associated with illness or other adverse effects resulting from patients' use or misuse of our products or any similar products distributed by other companies could have a material adverse impact on our results of operations.

We do not currently hold product liability insurance coverage. Prior to commercialization of our product candidates, we will need to purchase insurance coverage. As a result, we may be unable to maintain or obtain sufficient insurance at a reasonable cost to protect us against losses that could have a material adverse effect on our business. These liabilities could prevent or interfere with our product development and commercialization efforts. A successful product liability claim or series of claims brought against us, particularly if judgments exceed our insurance coverage, could decrease our cash resources and adversely affect our business, financial condition and results of operations.

Our employees, contractors, vendors and partners may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of fraud or other misconduct by our employees, contractors, vendors or partners. Misconduct by these parties could include failures to comply with FDA regulations, to provide accurate information to the FDA, to comply with federal and state healthcare fraud and abuse laws and regulations, to report financial information or data timely, completely or accurately, or to disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Third-party misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. We have adopted a Code of Business Conduct and Ethics, but it is not always possible to identify and deter misconduct, and the precautions we take to detect and prevent this activity may not be effective in

controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us resulting from this misconduct and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

We enter into various contracts in the normal course of our business in which we indemnify the other party to the contract. In the event we have to perform under these indemnification provisions, it could have a material adverse effect on our business, financial condition and results of operations.

In the normal course of business, we periodically enter into academic, commercial, service, collaboration, licensing, consulting and other agreements that contain indemnification provisions. With respect to our academic and other research agreements, we typically indemnify the institution and related parties from losses arising from claims relating to the products, processes or services made, used, sold or performed pursuant to the agreements for which we have secured licenses, and from claims arising from our or our potential sublicensees' exercise of rights under the agreements. With respect to our commercial agreements, we indemnify our vendors from any third-party product liability claims that could result from the production, use or consumption of the product, as well as for alleged infringements of any patent or other intellectual property right by a third party.

Should our obligation under an indemnification provision exceed applicable insurance coverage or if we are denied insurance coverage, our business, financial condition and results of operations could be adversely affected. Similarly, if we are relying on a collaborator to indemnify us and the collaborator is denied insurance coverage or the indemnification obligation exceeds the applicable insurance coverage, and if the collaborator does not have other assets available to indemnify us, our business, financial condition and results of operations could be adversely affected.

If we fail to develop and commercialize other product candidates, we may be unable to grow our business.

Although the development and commercialization of MGL-3196 is our primary focus, as part of our longer-term growth strategy, we plan to evaluate the development and commercialization of other therapies related to thyroid hormone, orphan and other diseases. We will evaluate internal opportunities from our compound libraries, and also may choose to in-license or acquire other product candidates as well as commercial products to treat patients suffering from thyroid hormone, orphan or other disorders with high unmet medical needs and limited treatment options. These other product candidates may require additional, time-consuming development efforts prior to commercial sale, including preclinical studies, clinical trials and approval by the FDA and/or applicable foreign regulatory authorities. All product candidates are prone to the risks of failure that are inherent in pharmaceutical product development, including the possibility that the product candidate will not be shown to be sufficiently safe and effective for approval by regulatory authorities. In addition, we cannot assure you that any such products that are approved will be manufactured or produced economically, be successfully commercialized, be widely accepted in the marketplace, or be more effective than other commercially available alternatives.

If we lose key management personnel, or if we fail to recruit additional highly skilled personnel, our ability to identify, develop and commercialize products will be impaired.

We are highly dependent on principal members of our management team, including our Chief Executive Officer, Paul A. Friedman, M.D., and our Chief Medical Officer, Rebecca Taub, M.D. These executives each have significant pharmaceutical industry experience. The loss of any member of

our management team or scientific staff, including Drs. Friedman and Taub, would impair our ability to identify, develop and market new products. Our management and other employees may voluntarily terminate their employment with us at any time. The loss of the services of these or other key personnel, or the inability to attract and retain additional qualified personnel, could result in delays to development or approval, loss of sales and diversion of management resources. In addition, we depend on our ability to attract and retain other highly skilled personnel. Competition for qualified personnel is intense, and the process of hiring and integrating such qualified personnel is often lengthy. We may be unable to recruit such personnel on a timely basis, if at all, which would negatively impact our development and commercialization programs.

Additionally, we do not currently maintain "key person" life insurance on the lives of our executives or any of our employees. This lack of insurance means that we may not receive adequate compensation for the loss of the services of these individuals.

We currently have no marketing, sales or distribution infrastructure with respect to our product candidates. If we are unable to develop our sales, marketing and distribution capabilities on our own or through collaborations with marketing partners, we will not be successful in commercializing our product candidates.

We currently have no marketing, sales or distribution capabilities and have limited sales or marketing experience within our organization. If our product candidate, MGL-3196, is approved, we intend either to establish a sales and marketing organization with technical expertise and supporting distribution capabilities to commercialize MGL-3196, or to outsource this function to a third party. Either of these options would be expensive and time-consuming. Some or all of these costs may be incurred in advance of any approval of MGL-3196. In addition, we may not be able to hire a sales force in the United States that is sufficient in size or has adequate expertise in the medical markets that we intend to target. Any failure or delay in the development of our internal sales, marketing and distribution capabilities would adversely affect the commercialization of MGL-3196 and other future product candidates.

With respect to our existing and future product candidates, we may choose to collaborate with third parties that have direct sales forces and established distribution systems, either to augment our own sales force and distribution systems or as an alternative to our own sales force and distribution systems. To the extent that we enter into co-promotion or other licensing arrangements, our product revenue may be lower than if we directly marketed or sold any approved products. In addition, any revenue we receive will depend in whole or in part upon the efforts of these third parties, which may not be successful and are generally not within our control. If we are unable to enter into these arrangements on acceptable terms or at all, we may not be able to successfully commercialize any approved products. If we are not successful in commercializing any approved products, either on our own or through collaborations with one or more third parties, our future product revenue will suffer and we may incur significant additional losses.

Even if we obtain FDA approval of MGL-3196 or any other future product candidate, we or our partners may never obtain approval or commercialize our products outside of the United States, which would limit our ability to realize their full market potential.

In order to market any products outside of the United States, we must establish and comply with numerous and varying regulatory requirements of other countries regarding clinical trial design, safety and efficacy. Clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not mean that regulatory approval will be obtained in any other country. Approval procedures vary among countries and can involve additional product testing and validation and additional administrative review periods. Seeking foreign regulatory approvals could result in significant delays, difficulties and costs for us

and may require additional preclinical studies or clinical trials which would be costly and time consuming. Regulatory requirements can vary widely from country to country and could delay or prevent the introduction of our products in those countries. Satisfying these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. In addition, our failure to obtain regulatory approval in any country may delay or have negative effects on the process for regulatory approval in other countries. We and our partners do not have any product candidates approved for sale in any jurisdiction, including international markets, and we do not have experience in obtaining regulatory approval in international markets. If we or our partners fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals, our target market will be reduced and our ability to realize the full market potential of our products will be harmed.

If we do not obtain protection under the Hatch-Waxman Amendments and similar foreign legislation by extending the term of patents covering each of our product candidates, our business may be materially harmed.

Depending upon the timing, duration and conditions of FDA marketing approval of our product candidates, one or more of our United States patents may be eligible for limited patent term extension under Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent term extension of up to five years for a patent covering an approved product as compensation for effective patent term lost during product development and the FDA regulatory review process. However, we may not receive an extension if we fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Moreover, the length of the extension could be less than we request. If we are unable to obtain patent term extension or the term of any such extension is less than we request, the period during which we can enforce our patent rights for that product may not extend beyond the current patent expiration dates and our competitors may obtain approval to market competing products sooner. As a result, our revenue could be potentially materially reduced. Further, if this occurs, our competitors may take advantage of our investment in development and trials by referencing our clinical and preclinical data and launch their product earlier than might otherwise be the case.

We may fail to obtain orphan drug designations from the FDA for our product candidates, as applicable, and even if we obtain such designations, we may be unable to maintain the benefits associated with orphan drug designation, including the potential for market exclusivity.

Our strategy includes filing for orphan drug designation where available for our product candidates. Under the Orphan Drug Act, the FDA may grant orphan drug designation to a drug or biologic intended to treat a rare disease or condition, which is defined as one occurring in a patient population of fewer than 200,000 in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug or biologic will be recovered from sales in the United States. In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. In addition, if a product that has orphan drug designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications, including a full NDA, to market the same drug or biologic for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or where the manufacturer is unable to assure sufficient product quantity.

We have not obtained orphan designation for any product candidates to date, although we believe some of the potential indications of our product candidates could qualify for orphan drug designation and the related benefits if approved for such indications and we may file for orphan drug designation with respect to such indications. Even if we obtain such designations, we may not be the first to obtain regulatory approval of a product candidate for the orphan-designated indication due to the uncertainties associated with developing pharmaceutical products. In addition, exclusive marketing rights in the United States may be limited if we seek approval for an indication broader than the orphan-designated indication or may be lost if the FDA later determines that the request for designation was materially defective or if we are unable to assure sufficient quantities of the product to meet the needs of patients with the orphan-designated disease or condition. Further, even if we obtain orphan drug designation exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs with different active moieties may receive and be approved for the same condition, and only the first applicant to receive approval will receive the benefits of marketing exclusivity. Even after an orphan-designated product is approved, the FDA can subsequently approve a later drug with the same active moiety for the same condition if the FDA concludes that the later drug is clinically superior if it is shown to be safer, more effective or makes a major contribution to patient care. Orphan drug designation neither shortens the development time or regulatory review time of a drug, nor gives the drug any advantage in the regulatory review or approval process. In addition, while we may seek orphan drug designation for our product candidates, we may never receive such designations. Failure to obtain an orphan drug designation for our product candidates may have a material adverse effect on our business, results of operations and financial condition.

If we or our partners market products in a manner that violates fraud and abuse and other healthcare laws, or if we or our partners violate government price reporting laws, we or our partners may be subject to administrative civil and/or criminal penalties.

Although we do not currently have any products on the market, if we obtain FDA approval for our product candidates, and begin commercializing those products in the United States, our operations may be directly, or indirectly through our prescribers, customers and third-party payors, subject to various U.S. federal and state healthcare laws and regulations. These laws include, among others, the U.S. federal Anti-Kickback Statute and the U.S. federal civil and criminal false claims laws. At such time, if ever, as we or any of our partners market any of our future approved products, it is possible that some of our business activities and/or our partners could be subject to challenge under one or more of these laws.

Federal false claims, false statements and civil monetary penalties laws prohibit, among others, any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, or causing to be made, a false statement to get a false claim paid. The federal healthcare program Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce, or in return for, purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item or service reimbursable under Medicare, Medicaid or other federally financed healthcare programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers, on the one hand, and prescribers, purchasers and formulary managers, on the other. Although there are several statutory exceptions and regulatory safe harbors protecting certain common activities from prosecution, the exceptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchasing or recommending may be subject to scrutiny if they do not qualify for an exception or safe harbor.

In addition, we and/or our partners may be subject to patient data privacy and security regulation, including the Health Insurance Portability and Accountability Act of 1996, as amended

by the Health Information Technology for Economic and Clinical Health Act, and their respective implementing regulations, which impose specified requirements relating to the privacy, security and transmission of individually identifiable health information.

Most states also have statutes or regulations similar to these federal laws, which may apply to items such as pharmaceutical products and services reimbursed by private insurers. We and/or our partners may be subject to administrative, civil and criminal sanctions for violations of any of these federal and state laws. Pharmaceutical and other healthcare companies have been prosecuted under these laws for a variety of promotional and marketing activities, such as: providing free trips, free goods, sham consulting fees and grants and other monetary benefits to prescribers; reporting to pricing services inflated average wholesale prices that were then used by federal programs to set reimbursement rates; engaging in off-label promotion; and submitting inflated best price information to the Medicaid Rebate Program to reduce liability for Medicaid rebates.

Ensuring that our internal operations and future business arrangements with third parties comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations, agency guidance or case law involving applicable fraud and abuse or other healthcare laws and regulations.

If the third parties on which we rely for the conduct of our clinical trials and results do not perform our clinical trial activities in accordance with good clinical practices and related regulatory requirements, we may be unable to obtain regulatory approval for or commercialize our product candidates.

We use third-party service providers to conduct and/or oversee the clinical trials of our product candidates and expect to continue to do so for the foreseeable future. We rely heavily on these parties for successful execution of our clinical trials. Nonetheless, we are responsible for confirming that each of our clinical trials is conducted in accordance with FDA requirements and our general investigational plan and protocol.

The FDA requires us and our third-party service providers to comply with regulations and standards, commonly referred to as good clinical practices, or GCP, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate, and that the trial participants are adequately protected. Our reliance on third parties that we do not control does not relieve us of these responsibilities and requirements. Third parties may not complete activities on schedule or may not conduct our clinical trials in accordance with regulatory or GCP requirements or the respective trial plans and protocols. In addition, third parties may not be able to repeat their past successes in clinical trials. The failure of these third parties to carry out their obligations could delay or prevent the development, approval and commercialization of our product candidates or result in enforcement action against us.

If our relationship with these third-party providers terminates, we may not be able to enter into arrangements with alternative providers or do so on commercially reasonable terms. Switching or adding additional third-party providers involves substantial cost and requires management time and focus, and could delay development and commercialization of our product candidates. Though we intend to carefully manage our relationships with our third-party providers, there can be no assurance that we will not encounter challenges or delays in the future or that these delays or challenges will not have a negative impact on our business and financial condition.

We have relied on, and expect to continue to rely on, third-party manufacturers to produce our product candidates.

We do not own or operate manufacturing facilities for the production of clinical or commercial quantities of our product candidates, and we lack the resources and the capabilities to do so. As a result, we currently rely, and expect to rely for the foreseeable future, on third-party manufacturers to supply our product candidates. Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured our product candidates or products ourselves, including:

- reliance on third-parties for manufacturing process development, regulatory compliance and quality assurance;
- limitations on supply availability resulting from capacity and scheduling constraints of third-parties;
- the possible breach of manufacturing agreements by third-parties because of factors beyond our control; and
- the possible termination or non-renewal of manufacturing agreements by third-parties, at a time that is costly or inconvenient to us.

If we do not maintain our key manufacturing relationships, we may fail to find replacement manufacturers or develop our own manufacturing capabilities, which could delay or impair our ability to obtain regulatory approval for our products and substantially increase our costs or deplete profit margins, if any. If we do find replacement manufacturers, we may not be able to enter into agreements with them on terms and conditions favorable to us and there could be a substantial delay before new facilities could be qualified and registered with the FDA and other foreign regulatory authorities.

The FDA and other foreign regulatory authorities require manufacturers to register manufacturing facilities. The FDA and corresponding foreign regulators also inspect these facilities to confirm compliance with current good manufacturing practices, or cGMPs. Contract manufacturers may face manufacturing or quality control problems causing drug substance production and shipment delays or a situation where the contractor may not be able to maintain compliance with the applicable cGMP requirements. Any failure to comply with cGMP requirements or other FDA, European Medicines Agency, or EMA, and comparable foreign regulatory requirements could adversely affect our clinical research activities and our ability to develop our product candidates and market our products following approval.

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

We previously identified a material weakness in our internal control over financial reporting and may identify additional material weaknesses in the future or otherwise fail to maintain an effective system of internal controls, which may result in material misstatements of our financial statements or cause us to fail to meet our reporting obligations or fail to prevent fraud; and in that case, our stockholders could lose confidence in our financial reporting, which would harm our business and could negatively impact the price of our stock.

Effective internal controls are necessary for us to provide reliable financial reports and prevent fraud. If we fail to maintain an effective system of internal controls, we may be unable to report our financial results accurately or prevent fraud; and, in that case, our stockholders could lose confidence in our financial reporting, which would harm our business and could negatively impact

the price of our stock. On March 31, 2017, we filed with the SEC an amendment to our Quarterly Report on Form 10-Q for the quarter ended September 30, 2016 to correct certain errors therein. Management reported a material weakness in our system of internal controls over financial reporting as of September 30, 2016. A material weakness is a deficiency, or combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of our annual or interim financial statements will not be prevented or detected on a timely basis. We remediated this material weakness. We cannot assure you that the measures we have taken to date will be sufficient to avoid future material weaknesses. Even when we conclude that our internal control over financial reporting provides reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with U.S. generally accepted accounting principles, or GAAP, because of its inherent limitations, internal control over financial reporting may not prevent or detect fraud or misstatements.

Our reporting obligations as a public company will require significant managerial, operational and financial resources for the foreseeable future. If we fail to maintain the adequacy of our internal control over financial reporting, we may not be able to produce reliable financial reports or help prevent fraud. Our failure to maintain effective internal control over financial reporting could prevent us from filing our periodic reports on a timely basis which could result in the loss of investor confidence in the reliability of our financial statements, harm our business and negatively impact the trading price of our common stock.

Risks Relating to Our Intellectual Property

Our rights to develop and commercialize our product candidates are subject in part to the terms and conditions of a license to MGL-3196 granted to us by Roche.

We entered into the Roche Agreement, with Roche, on December 18, 2008. Pursuant to the terms of the Roche Agreement, we assumed control of all development and commercialization of MGL-3196 and hold exclusive worldwide rights for all potential indications. Under the Roche Agreement, Roche exclusively licensed certain patent rights and know-how relating to MGL-3196 in exchange for consideration consisting of an upfront payment, milestone payments tied to the achievement of product development and regulatory milestones, and royalty payments based on net sales of products containing MGL-3196 or another licensed product, subject to certain reductions. We must use commercially reasonable efforts to conduct clinical and commercial development programs for products containing MGL-3196. If we determine that it is not reasonable to continue clinical trials or other development of MGL-3196, we may elect to cease further development and Roche may terminate the license. If we determine not to pursue the development or commercialization of MGL-3196 in certain jurisdictions, including the United States, Roche may terminate the license for such territories. The Roche Agreement will expire, unless earlier terminated pursuant to other provisions thereof, on the last to occur of (i) the expiration of the last valid claim of a licensed patent covering the manufacture, use or sale of products containing MGL-3196, or (ii) ten years after the first sale of a product containing MGL-3196.

Under the Roche Agreement, Roche controls prosecution of the licensed patent rights, although we have a right to comment.

We do not have, nor have we had, any material disputes with Roche regarding the Roche Agreement. However, if there is any future dispute between us and Roche regarding the parties' rights under the Roche Agreement, our ability to develop and commercialize MGL-3196, or any other product candidate covered by the Roche Agreement, may be materially harmed. Any uncured, material breach under the Roche Agreement could result in our loss of exclusive rights to MGL-3196 and may lead to a complete termination of the Roche Agreement and force us to cease product development efforts for MGL-3196.

We may fail to comply with any of our obligations under agreements pursuant to which we license rights or technology, which could result in the loss of rights or technology that are material to our business.

We may enter into license agreements from time to time. Licensing of intellectual property is important to our business and involves complex legal, business and scientific issues. Disputes may arise regarding intellectual property subject to a license agreement, including but not limited to:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property by us and our licensors and collaborators; and
- the priority of invention of patented technology.

If disputes over intellectual property and other rights that we have licensed or acquired from third parties prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates.

Our success depends on our ability to protect our intellectual property and our proprietary technologies.

Our success depends on our ability to protect our intellectual property and our proprietary technologies. Our commercial success depends in part on our ability to obtain and maintain patent protection and trade secret protection for our product candidates, proprietary technologies, and their uses, as well as our ability to operate without infringing upon the proprietary rights of others.

We can provide no assurance that our patent applications or those of our licensors will result in additional patents being issued or that issued patents will afford sufficient protection against competitors with similar technologies, nor can we provide any assurance that the patents issued will not be infringed, designed around or invalidated by third parties. Even issued patents may later be found unenforceable or may be modified or revoked in proceedings instituted by third parties before various patent offices or in courts. The degree of future protection for our proprietary rights is uncertain. Only limited protection may be available and may not adequately protect our rights or permit us to gain or keep any competitive advantage. This failure to properly protect the intellectual property rights relating to our product candidates could have a material adverse effect on our financial condition and results of operations. Composition-of-matter patents on the biological or chemical active pharmaceutical ingredients are generally considered to offer the strongest protection of intellectual property and provide the broadest scope of patent protection for pharmaceutical products, as such patents provide protection without regard to any method of use or any method of manufacturing. While we have licensed rights to issued composition-of-matter patents in the United States and other jurisdictions for MGL-3196, we cannot be certain that the claims in issued composition-of-matter patents will not be found invalid or unenforceable if challenged. We cannot be certain that the claims in owned and licensed patent applications covering our product candidates will be considered patentable by the United States Patent and Trademark Office, or USPTO, and valid by courts in the United States or by the patent offices and

courts in foreign jurisdictions. Even if we owned and licensed patent applications covering our product candidates, the patents may not be enforced against competitors. For example, a formulation patent will not be enforced against those making and marketing a product that has the same active pharmaceutical ingredient in a different formulation that is not claimed in the formulation patent. Method-of-use patents protect the use of a product for the specified method or for treatment of a particular indication. This type of patent may not be enforced against competitors making and marketing a product that has the same active pharmaceutical ingredient but is used for a method not claimed in the patent. Moreover, even if competitors do not actively promote their product for our targeted indications, physicians may prescribe these products "off-label." Although off-label prescriptions may infringe or contribute to the infringement of method-of-use patents, the practice is common and such infringement is difficult to prevent or prosecute.

Our licensed composition-of-matter patent licensed from Roche for MGL-3196 is expected to expire in the United States in 2026. Our co-owned patents and pending patent applications that cover our particular solid form, dosage, method of manufacturing, and uses of MGL-3196 to treat various indications are expected to expire in 2033. While patent term adjustments or patent term extensions could result in later expiration dates for each of these patents, there can be no assurances that we will receive any patent adjustments or patent term extensions. The patent application process and patent maintenance and enforcement are subject to numerous risks and uncertainties, and there can be no assurance that we or any of our future development partners will be successful in protecting our product candidates by obtaining and defending patents. These risks and uncertainties include the following:

- the USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions during the patent process and after a patent has issued. There are situations in which noncompliance can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, competitors might be able to enter the market earlier than would otherwise have been the case;

- patent applications may not result in any patents being issued;

- patents may be challenged, invalidated, modified, revoked, circumvented, found to be unenforceable or otherwise may not provide any competitive advantage;

- we and our licensor(s) may not have been the first to make the inventions covered by pending patent applications or issued patents;

- we and our licensor(s) may not have been the first to file patent applications for our product candidates or the compositions developed, or for their uses;

- others may independently develop identical, similar or alternative products or compositions and uses thereof;

- we and our licensor(s)' disclosures in patent applications may not be sufficient to meet the statutory requirements for patentability;

- others may design around our owned and licensed patent claims to produce competitive products which fall outside of the scope of the patents;

- others may identify prior art or other bases which could invalidate our or licensor(s)' patents;

- our competitors might conduct research and development activities in the United States and other countries that provide a safe harbor from patent infringement claims for certain research and development activities, as well as in countries where us and our licensor(s) do

not have patent rights, and then use the information learned from such activities to develop competitive products for sale in major commercial markets;

- there may be significant pressure on the United States government and international governmental bodies to limit the scope of patent protection both inside and outside the United States for disease treatments that prove successful, as a matter of public policy regarding worldwide health concerns; and

- countries other than the United States may have patent laws less favorable to patentees than those upheld by United States courts, allowing foreign competitors a better opportunity to create, develop and market competing product candidates.

In addition, we rely on the protection of our trade secrets and proprietary know-how. Although we have taken steps to protect our trade secrets and unpatented know-how, including entering into confidentiality agreements with third parties, and confidential information and inventions agreements with employees, consultants and advisors, we cannot provide any assurances that any of these parties would not breach the agreements to disclose any proprietary information, including trade secrets, and we may not be able to obtain adequate remedies for such breaches. Further, third parties may still obtain this information by other means, such as breaches of our physical or computer security systems. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. Moreover, third parties may come upon this or similar information lawfully and independently. We would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. Further, intellectual property rights have limitations and do not necessarily address all potential threats to our competitive position. If any of these events occurs or if we otherwise lose protection for our trade secrets or proprietary know-how, our business may be harmed.

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. In particular, under the Leahy-Smith Act, the United States transitioned in March 2013 to a "first inventor to file" system in which the first inventor to file a patent application will be entitled to the patent. Third parties are allowed to submit prior art before the issuance of a patent by the USPTO, and a patent may become subject to post-grant proceedings including opposition, derivation, reexamination, *inter partes* review or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope or enforceability of, or invalidate, our patent rights, which could adversely affect our competitive position.

Claims by third parties that we infringe their proprietary rights may result in liability for damages or prevent or delay our developmental and commercialization efforts.

The biotechnology industry has been characterized by frequent litigation regarding patent and other intellectual property rights. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are developing product candidates. As the biotechnology industry expands and more patents are issued, the risk increases that our product candidates may be subject to claims of infringement of the patent rights of third parties. Because patent applications are maintained in secrecy until the application is published, we may be unaware of third party patents that may be infringed by commercialization of

MGL-3196 or our other product candidates. Moreover, because patent applications can take many years to issue, there may be currently-pending patent applications that may later result in issued patents that our product candidates may infringe. In addition, identification of third party patent rights that may be relevant to our technology is difficult because patent searching is imperfect due to differences in terminology among patents, incomplete databases and the difficulty in assessing the meaning of patent claims. Any claims of patent infringement asserted by third parties would be time consuming and could likely:

- result in costly litigation;
- divert the time and attention of our technical personnel and management;
- cause development delays;
- prevent us from commercializing MGL-3196 for NASH or FH or our other product candidates until the asserted patent expires or is held finally invalid or not infringed in a court of law;
- require us to develop non-infringing technology, which may not be possible on a cost-effective basis; or
- require us to enter into royalty or licensing agreements.

Although no third party has asserted a claim of patent infringement against us as of the filing date of this report, others may hold proprietary rights that could prevent MGL-3196 or our other product candidates from being marketed. Any patent-related legal action against us claiming damages and seeking to enjoin commercial activities relating to our product candidate or processes could subject us to potential liability for damages and require us to obtain a license to continue to manufacture or market MGL-3196 or our other product candidates. We cannot predict whether we would prevail in any such actions or that any license required under any of these patents would be made available on commercially acceptable terms, if at all. In addition, we cannot be sure that we could redesign our product candidate or processes to avoid infringement, if necessary. Accordingly, an adverse determination in a judicial or administrative proceeding, or the failure to obtain necessary licenses, could prevent us from developing and commercializing MGL-3196 or our other product candidates, which could harm our business, financial condition and operating results.

Moreover, we may be subject to a third party preissuance submission of prior art to the USPTO or in addition to interference proceedings, may become involved in opposition, derivation, reexamination, *inter partes* review, post-grant review or other post-grant proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time consuming, and unsuccessful. Further, our issued patents could be found invalid or unenforceable if challenged in court.

If we or any of our future development partners were to initiate legal proceedings against a third party to enforce a patent directed at one of our product candidates, or one of our future product candidates, the defendant could counterclaim that our patent is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity

and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, non-enablement or insufficient written description. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO or made a misleading statement during prosecution. Third parties may also raise similar claims before the USPTO, even outside the context of litigation. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on such product candidate. Such a loss of patent protection would have a material adverse impact on our business.

Interference proceedings provoked by third parties or brought by us or declared by the USPTO may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. In addition, the uncertainties associated with litigation could have a material adverse effect on our ability to raise the funds necessary to continue our clinical trials, continue our research programs, license necessary technology from third parties, or enter into development partnerships that would help us bring our product candidates to market.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions, or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock.

We may not be successful in obtaining or maintaining necessary rights to our product candidates through acquisitions and in-licenses.

We currently have rights to the intellectual property, through licenses from third parties and under patents that we own or co-own, to develop our product candidates. Because our programs may require the use of proprietary rights held by third parties, the growth of our business may depend in part on our ability to acquire, in-license, or use these proprietary rights. For example, our product candidates may require specific formulations to work effectively and efficiently and the rights to these formulations may be held by others. We may be unable to acquire or in-license any compositions, methods of use, processes, or other third party intellectual property rights from third parties that we identify as necessary for our product candidates. The licensing and acquisition of third party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire third party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources, and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third party intellectual property rights on terms that would allow us to make an appropriate return on our investment.

We may collaborate with U.S. and foreign academic institutions and industry collaborators to accelerate our preclinical or clinical research. Typically, these institutions provide us with an option

to negotiate a license to any of the institution's rights in technology resulting from the collaboration. Regardless of such option, we may be unable to negotiate a license within the specified timeframe or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program.

If we are unable to successfully obtain rights to required third party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of that program and our business and financial condition could suffer.

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we rely on third parties to research and develop and to manufacture our product candidates, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, consulting agreements or other similar agreements with our advisors, employees, third party contractors and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, including our trade secrets. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Any of these could impair our competitive position.

In addition, these agreements typically restrict the ability of our advisors, employees, third party contractors and consultants to publish data potentially relating to our trade secrets, although our agreements may contain certain limited publication rights. For example, any academic institution that we may collaborate with in the future will usually expect to be granted rights to publish data arising out of such collaboration, provided that we are notified in advance and given the opportunity to delay publication for a limited time period in order for us to secure patent protection of intellectual property rights arising from the collaboration, in addition to the opportunity to remove confidential or trade secret information from any such publication. In the future we may also conduct joint research and development programs that may require us to share trade secrets under the terms of our research and development or similar agreements. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of our agreements with third parties, independent development or publication of information by any of our third party collaborators. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business.

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

Our registered or unregistered trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our registered or unregistered trademarks or trade names. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely impact our financial condition or results of operations.

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

While we have licensed from Roche issued composition-of-matter patents directed at MGL-3196 in the United States and other countries, filing, prosecuting and defending patents on MGL-3196 in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some foreign countries may not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing their inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection but enforcement is not as strong as that in the United States. These products may compete with MGL-3196, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

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

Risks Related to Our Financial Position and Need for Capital

If we fail to obtain the capital necessary to fund our operations, we will be unable to successfully develop and commercialize MGL-3196 and other future product candidates.

Although we believe that our existing cash and cash equivalents will be sufficient to fund our current operations through at least the next 12 months, we may require additional working capital in order to complete the remaining clinical development for MGL-3196 and our other product candidates through potential regulatory approval and through potential commercialization of these product candidates. In particular, in order to initiate our Phase 3 clinical program for MGL-3196 in NASH, we may need to collaborate with a strategic partner or raise additional working capital. We expect our spending levels to increase in connection with our clinical trials of MGL-3196 as well as other corporate activities. The amount and timing of any expenditure needed to implement our development and commercialization programs will depend on numerous factors, including:

- the type, number, scope, progress, expansion costs, results of and timing of our ongoing or future clinical trials or the need for additional clinical trials of MGL-3196 for NASH and FH or any of our other product candidates which we are pursuing or may choose to pursue in the future;

- the costs of obtaining, maintaining and enforcing our patents and other intellectual property rights;

- the costs and timing of obtaining regulatory approval for MGL-3196 for NASH and FH and any of our other product candidates;
- the costs and timing of obtaining or maintaining manufacturing for MGL-3196 for NASH and FH and any of our other product candidates, including commercial manufacturing if any product candidate is approved;
- the costs and timing of establishing sales, marketing and reimbursement capabilities and enhanced internal controls over financial reporting;
- the terms and timing of establishing and maintaining collaborations, license agreements and other partnerships;
- costs associated with any new product candidates that we may develop, in-license or acquire;
- the effect of competing technological and market developments; and
- the costs associated with operating as a public company.

Some of these factors are outside of our control. We do not expect our existing capital resources to be sufficient to enable us to fund the completion of our clinical trials and commercialization of our product candidates. We expect that we will need to raise substantial additional funds in the future.

We have not sold any products, and we do not expect to sell or derive revenue from any product sales for the foreseeable future. We may seek additional funding through future debt and equity financings, as well as potential additional collaborations or strategic partnerships with other companies or through non-dilutive financings. Additional funding may not be available to us on acceptable terms or at all. In addition, the terms of any financing may adversely affect the holdings or the rights of our stockholders. In addition, the issuance of additional shares by us, or the possibility of such issuance, may cause the market price of our shares to decline.

If we are unable to obtain additional funding on a timely basis, we may be unable to complete ongoing and planned clinical trials for MGL-3196 for NASH and FH and any of our other product candidates, and we may be required to significantly curtail some or all of our activities. We also could be required to seek funds through arrangements with collaborative partners or otherwise that may require us to relinquish rights to our product candidates or otherwise agree to terms unfavorable to us.

Our ability to use net operating loss and tax credit carryforwards and certain built-in losses to reduce future tax payments may be limited by provisions of the Internal Revenue Code.

Our net operating losses have been fully offset by a valuation allowance due to uncertainties surrounding our ability to realize these tax benefits. Under Section 382 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an "ownership change" (generally defined as a greater than 50% change (by value) in its equity ownership over a three year period), the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change income may be limited. Similar rules may apply under state tax laws. We have not performed a detailed analysis to determine whether an ownership change under Section 382 of the Code, or similar state provisions, has previously occurred. As a result, if we earn net taxable income, our ability to use our pre-change net operating loss carryforwards to offset U.S. federal taxable income may become subject to limitations, which could potentially result in increased future tax liability to us and may be substantial.

Risks Relating to Ownership of Our Common Stock

The price of our common stock has been, and may continue to be, volatile.

Historically, the market price of our common stock has fluctuated over a wide range, and it is likely that the price of our common stock will continue to be volatile in the future. The market price of our common stock could be impacted due to a variety of factors, including, in addition to global and industry-wide events:

- the losses we may incur;
- developments in patent or other proprietary rights owned or licensed by us, our collaborative partners or our competitors;
- public concern as to the safety and efficacy of products developed by us or others; and
- litigation.

In addition, due to one or more of the foregoing factors in one or more future quarters, our results of operations may fall below the expectations of securities analysts and investors. In that event, the market price of our common stock could materially decline.

A small number of our stockholders beneficially own a substantial amount of our common stock and have substantial control over us; therefore, your ability to influence corporate matters may be limited.

Certain stockholders affiliated with our officers and directors collectively beneficially own or control approximately 44.8% of our outstanding common stock as of March 31, 2018 and acting together, may have the ability to affect matters submitted to our stockholders for approval. This concentration of ownership may have the effect of delaying, deferring or preventing a strategic transaction, even if such a transaction would benefit other stockholders.

Anti-takeover provisions in our charter documents and under Delaware law could make an acquisition of our company, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our charter and bylaws may delay or prevent a merger, acquisition or other change of control that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions include a classified board of directors. In addition, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits, with some exceptions, stockholders owning in excess of 15% of our outstanding voting stock from merging or combining with us. Although we believe these provisions together provide for an opportunity to receive higher bids by requiring potential acquirers to negotiate with our board of directors, they would apply even if the offer may be considered beneficial by some stockholders.

Future sales and issuances of our common stock or rights to purchase common stock could result in additional dilution of the percentage ownership of our stockholders and could cause our share price to fall.

We expect that significant additional capital will be needed in the future to continue our planned operations. To the extent we raise additional capital by issuing equity securities, our stockholders may experience substantial dilution. We may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities in more than one transaction, investors may be materially diluted by subsequent sales. Such sales may also

result in material dilution to our existing stockholders, and new investors could gain rights superior to our existing stockholders.

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

Sales of a substantial number of shares of our common stock in the public market by us, by our existing stockholders, or by the holders of our Series A Convertible Preferred Stock upon conversion, or the perception that these sales might occur, could significantly reduce the market price of our common stock and impair our ability to raise adequate capital through the sale of additional equity securities.

We do not anticipate paying cash dividends on our common stock, and accordingly, stockholders must rely on stock appreciation for any return on their investment.

We have never declared or paid any cash dividend on our common stock and do not anticipate paying cash dividends on our common stock in the future. As a result, the only return to stockholders will be appreciation in the price of our common stock, which may never occur. Investors seeking cash dividends should not invest in our common stock.

Risks Related to Stockholders' Sales of Shares, Including Those Issued under the Securities Purchase Agreement

Sales of a significant number of shares of our common stock in the public markets or significant short sales of our common stock, or the perception that such sales could occur, could depress the market price of our common stock and impair our ability to raise capital.

As of March 31, 2018, there were 1,969,797 shares of Series A Convertible Preferred stock outstanding, all of which are readily convertible into common stock at the option of the holders. In addition, there are an additional 1,122,585 shares of our common stock issuable upon the exercise of outstanding stock options. Sales of a substantial number of shares of our common stock or other equity-related securities in the public markets, could depress the market price of our common stock. If there are significant sales or short sales of our stock, the price decline that could result from this activity may cause the share price to decline further, which, in turn, may cause long holders of the common stock to sell their shares, thereby contributing to sales of common stock in the market. Such sales also may impair our ability to raise capital through the sale of additional shares in the future at a time and price that our management deems acceptable, if at all.

Risks Related to This Offering

Investors in this offering will pay a much higher price than the book value of our common stock.

If you purchase common stock in this offering, you will incur an immediate and substantial dilution of $248.83 per share, representing the difference between an assumed public offering price of $273.24 per share (the last reported sale price of our common stock on The Nasdaq Global Market on June 4, 2018) and our as adjusted net tangible book value per share after giving effect to this offering, and after deducting underwriting discounts and commissions for shares sold in this offering and estimated offering expenses payable by us. See "Dilution." To the extent outstanding options or warrants we have issued are ultimately exercised, you will incur additional dilution. Furthermore, if the underwriter exercises its option to purchase additional shares, you will also incur additional dilution.

Our management will have broad discretion over the use of the net proceeds from this offering; you may not agree with how we use the proceeds and the proceeds may not be invested successfully.

Our management will have broad discretion as to the use of the net proceeds from this offering by us and could use them for purposes other than those contemplated at the time of this offering. Accordingly, you may be relying on the judgment of our management with regard to the use of these net proceeds, and you will not have the opportunity, as part of your investment decision, to assess whether the proceeds are being used appropriately. It is possible that the proceeds will be invested in a way that does not yield a favorable, or any, return for us.

Sales of additional shares of our common stock, including by us or our directors, officers and significant stockholders following expiration or early release of the 90-day lock-up, could cause the price of our common stock to decline.

Sales of substantial amounts of our common stock in the public market, or the availability of such shares for sale, by us or others, including the issuance of common stock upon exercise of outstanding options or upon the conversion of our Series A Convertible Preferred Stock, could adversely affect the price of our common stock. Based on the total number of outstanding shares of our common stock as of March 31, 2018, upon completion of this offering, we will have 14,982,683 outstanding shares of common stock. In connection with this offering, we, our directors and officers and certain of our significant stockholders have entered into lock-up agreements with the underwriter under which we, our directors and officers and significant stockholders have agreed, subject to specific exceptions described in the section titled "Underwriting", not to sell, directly or indirectly, any shares of common stock without the permission of Goldman Sachs & Co. LLC for a period of 90 days following the date of this prospectus supplement. Upon expiration or earlier release of the lock-up, we, our directors or officers or significant stockholders may sell shares into the market, which could adversely affect the market price of shares of our common stock. Sales of a substantial number of such shares upon expiration of the lock-up agreements, the perception that such sales may occur, or early release of these agreements, could cause our market price to fall or make it more difficult for you to sell your common stock at a time and price that you deem appropriate.

SPECIAL NOTE REGARDING FORWARD-LOOKING INFORMATION

This prospectus supplement, the accompanying prospectus, and the documents we incorporate by reference herein and therein include forward-looking statements within the meaning of the federal securities laws, which statements are subject to substantial risks and uncertainties. These forward-looking statements are intended to qualify for the safe harbor from liability established by the Private Securities Litigation Reform Act of 1995. All statements other than statements of historical fact are forward-looking statements. We have attempted to identify forward-looking statements by using words such as "may," "believe," "will," "could," "project," "anticipate," "expect," "estimate," "should," "continue," "potential," "plan," "forecasts," "goal," "seek," "intend," other forms of these words or similar words or expressions or the negative thereof.

In particular, this prospectus supplement, and the documents we incorporate by reference in this prospectus supplement, contain forward-looking statements relating to, among other things:

- Anticipated or estimated future results, including the risks and uncertainties associated with our future operating performance and financial position;
- Market demand for and acceptance of our products;
- Research, development and commercialization of new products;
- Obtaining and maintaining regulatory approvals, including, but not limited to, potential regulatory delays or rejections;
- Risks associated with meeting the objectives of clinical studies, including, but not limited to, delays or failures in enrollment, and the occurrence of adverse safety events;
- Risks related to our ability to accomplish our business development objectives and realize the anticipated benefit of any such transactions; and
- Assumptions underlying any of the foregoing.

We have based our forward-looking statements on our expectations and projections about trends affecting our business and industry and other future events. Although we do not make forward-looking statements unless we believe we have a reasonable basis for doing so, we cannot guarantee their accuracy. Forward-looking statements are subject to substantial risks and uncertainties that could cause our future business, financial condition, results of operations or performance, to differ materially from our historical results or those expressed or implied in any forward-looking statement. Some of the risks and uncertainties that may cause actual results to differ from those expressed or implied in the forward-looking statements are described in the section entitled "Risk Factors" in this prospectus supplement, as well as in our other filings with the SEC. In addition, actual results may differ as a result of additional risks and uncertainties of which we are currently unaware or which we do not currently view as material to our business. For these reasons, investors are cautioned not to place undue reliance on any forward-looking statements.

USE OF PROCEEDS

We estimate that the net proceeds from the sale of shares of common stock that we are selling in this offering will be approximately $188.5 million based on the assumed sale of $200,000,000 of shares of our common stock offered hereby, or approximately $230.8 million if the underwriter exercises in full its option to purchase an assumed $44,900,000 of additional shares of common stock from us, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

We will not receive any of the proceeds from the sale of the shares of our common stock by the selling stockholders (including any shares sold by certain of the selling stockholders pursuant the underwriter's option to purchase additional shares). However, we have agreed to pay expenses incurred by the selling stockholders in connection with the offering, other than the underwriting discounts and commissions.

The principal purposes of this offering are to increase our financial flexibility, facilitate an orderly distribution of our shares by selling stockholders and increase our public float. We intend to use the net proceeds from this offering, if any, for general corporate purposes, including, without limitation, research and development expenditures, clinical trial expenditures, manufacture and supply of drug substance and drug products, acquisitions of new technologies, capital expenditures and working capital. We may temporarily invest the net proceeds in short-term, interest-bearing instruments or other investment-grade securities. We have not determined the amount of net proceeds to be used specifically for such purposes. As a result, management will retain broad discretion over the allocation of net proceeds.

DILUTION

If you purchase our common stock in this offering, your interest will be diluted to the extent of the difference between the public offering price per share and the net tangible book value per share of our common stock after this offering. We calculate net tangible book value per share by subtracting our total liabilities from our total tangible assets and dividing the difference by the number of outstanding shares of our common stock.

Our net tangible book value at March 31, 2018 was approximately $177.2 million, or $12.43 per share, based on 14,250,726 shares of our common stock then outstanding. Historical net tangible book value per share is equal to our total tangible assets, less total liabilities, divided by the number of outstanding shares of our common stock. Dilution in net tangible book value per share represents the difference between the amount per share paid by purchasers of shares of common stock in this offering and the net tangible book value per share of our common stock immediately after this offering.

After giving effect to the assumed sale by us of $200 million of shares of common stock in this offering at an assumed public offering price of $273.24 per share (the last reported sale price on The Nasdaq Global Market on June 4, 2018), less the underwriting discounts and commissions and estimated offering expenses payable by us, our pro forma net tangible book value at March 31, 2018 would be approximately $365.7 million, or $24.41 per share. This represents an immediate increase in net tangible book value of $11.97 per share to existing stockholders and an immediate dilution of $248.83 per share to investors in this offering. The following table illustrates this per share dilution:

Assumed public offering price per share		$ 273.24
Historical net tangible book value per share as of March 31, 2018	$ 12.43	
Increase in net tangible book value per share attributable to new investors purchasing shares in this offering	$ 11.97	
Pro forma net tangible book value per share after this offering		$ 24.41
Dilution per share to new investors		$ 248.83

The above discussion and table are based on 14,250,726 shares of our common stock outstanding as of March 31, 2018 and excludes the following:

- 1,969,797 shares of common stock issuable upon conversion of our Series A Convertible Preferred Stock outstanding as of March 31, 2018;
- 1,122,585 shares of our common stock issuable upon the exercise of options outstanding as of March 31, 2018, having a weighted average exercise price of $28.63 per share; and
- an aggregate of 1,289,595 shares of our common stock reserved for future issuance as of March 31, 2018 under our 2015 Stock Plan.

In addition, the amounts in the table above assume no exercise by the underwriter of its option to purchase additional shares of our common stock.

PRICE RANGE OF COMMON STOCK

Our common stock is listed on The Nasdaq Global Market under the symbol "MDGL." The following table shows the closing high and low per share sale prices of our common stock for the periods indicated.

	High	Low
Year Ending December 31, 2018:		
First Quarter	$ 154.75	$ 90.56
Second Quarter (through June 4, 2018)	$ 279.80	$ 98.81
Year Ending December 31, 2017:		
First Quarter	$ 16.39	$ 14.82
Second Quarter	$ 17.50	$ 13.11
Third Quarter	$ 46.19	$ 15.16
Fourth Quarter	$ 101.00	$ 38.82
Year Ended December 31, 2016:		
First Quarter	$ 11.90	$ 6.65
Second Quarter	$ 15.40	$ 8.05
Third Quarter	$ 12.68	$ 6.89
Fourth Quarter	$ 17.66	$ 12.81

On June 4, 2018, the closing price of our common stock on The Nasdaq Global Market was $273.24 per share, and there were 40 holders of record of our common stock.

DIVIDEND POLICY

We do not currently anticipate declaring or paying cash dividends on our capital stock in the foreseeable future. We currently intend to retain all of our future earnings, if any, to finance the operation and expansion of our business. Any future determination relating to our dividend policy will be made at the discretion of our board of directors and will depend on a number of factors, including future earnings, capital requirements, future prospects, contractual restrictions and covenants and other factors that our board of directors may deem relevant.

DESCRIPTION OF CAPITAL STOCK

The following is a summary of all material characteristics of our capital stock as set forth in our restated certificate of incorporation, our restated bylaws and our Certificate of Designation of Preferences, Rights and Limitations of Series A Convertible Preferred Stock. The summary does not purport to be complete and is qualified in its entirety by reference to our certificate of incorporation and bylaws, copies of which have been filed as exhibits to our previous SEC filings. For more information, see the sections entitled "Incorporation of Certain Documents by Reference" and "Where You Can Find More Information."

Description of Common Stock

We are authorized to issue 200,000,000 shares of common stock, par value $0.0001 per share. The following summary of certain provisions of our common stock does not purport to be complete. You should refer to our restated certificate of incorporation and our restated bylaws, both of which have been filed with the SEC. The summary below is also qualified by provisions of applicable law.

General

As of May 31, 2018, there were 14,250,726 shares of common stock outstanding. Holders of common stock are entitled to one vote for each share held of record on all matters submitted to a vote of the stockholders, and do not have cumulative voting rights. Subject to preferences that may be applicable to any outstanding shares of preferred stock, holders of common stock are entitled to receive ratably such dividends, if any, as may be declared from time to time by our board of directors out of funds legally available for dividend payments. The holders of common stock have no preferences or rights of conversion, exchange, pre-emption or other subscription rights. There are no redemption or sinking fund provisions applicable to the common stock. In the event of any liquidation, dissolution or winding-up of our affairs, holders of common stock will be entitled to share ratably in our assets that are remaining after payment or provision for payment of all of our debts and obligations and after liquidation payments to holders of outstanding shares of preferred stock, if any.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company N.A., whose address is Meidinger Tower, 462 South 4th Street, Louisville, KY 40202 and whose telephone number is (502) 301-6088.

Nasdaq Global Market

Our common stock is listed for quotation on The Nasdaq Global Market under the symbol "MDGL."

Dividends

We have never declared any cash dividends on our common stock and we do not anticipate paying any cash dividends on our common stock in the foreseeable future.

Description of Preferred Stock

We are authorized to issue 5,000,000 shares of preferred stock, par value $0.0001 per share. As of May 31, 2018, we had 1,969,797 shares of preferred stock, designated Series A Convertible Preferred Stock, outstanding held by two stockholders of record. No other shares of our preferred

stock were outstanding or designated. The following summary of certain provisions of our preferred stock does not purport to be complete. You should refer to our restated certificate of incorporation, our restated bylaws and our Certificate of Designation of Preferences, Rights and Limitations of Series A Convertible Preferred Stock, each of which have been filed with the SEC. The summary below is also qualified by provisions of applicable law.

General

Our board of directors may, without further action by our stockholders, from time to time, direct the issuance of shares of preferred stock in series and may, at the time of issuance, determine the rights, preferences and limitations of each series, including voting rights, dividend rights and redemption and liquidation preferences. Satisfaction of any dividend preferences of outstanding shares of preferred stock would reduce the amount of funds available for the payment of dividends on shares of our common stock. Holders of shares of preferred stock may be entitled to receive a preference payment in the event of any liquidation, dissolution or winding-up of our company before any payment is made to the holders of shares of our common stock. In some circumstances, the issuance of shares of preferred stock may render more difficult or tend to discourage a merger, tender offer or proxy contest, the assumption of control by a holder of a large block of our securities or the removal of incumbent management. Upon the affirmative vote of our board of directors, without stockholder approval, we may issue shares of preferred stock with voting and conversion rights which could adversely affect the holders of shares of our common stock.

Series A Convertible Preferred Stock

Each share of the Series A Convertible Preferred Stock is convertible into shares of the common stock at any time at the holder's option at a one-to-one ratio, subject to adjustment. The holder, however, will be prohibited from converting shares of the Series A Convertible Preferred Stock into shares of our common stock if, as a result of such conversion, the holder, together with its affiliates, would own more than 4.99% of the shares of our common stock or any other class of any equity security of ours (other than an exempted security) that is registered pursuant to Section 12 of the Securities Exchange Act of 1934, which may be increased or decreased to any other percentage at the holder's election on 61 days' notice delivered to the Company.

Upon our liquidation, dissolution or winding-up, whether voluntary or involuntary, after the satisfaction in full of our debts and the payment of any liquidation preference owed to the holders of shares of our capital stock ranking prior to the Series A Convertible Preferred Stock upon liquidation, the holders of the Series A Convertible Preferred Stock shall participate pari passu with the holders of our common stock (on an as-if-converted-to-common-stock basis) in our net assets. Shares of the Series A Convertible Preferred Stock will generally have no voting rights, except as required by law. Shares of the Series A Convertible Preferred Stock will be entitled to receive dividends before shares of any other class or series of our capital stock (other than dividends in the form of our common stock) equal to the dividend payable on each share of our common stock, on an as-converted basis.

Anti-Takeover Provisions of our Certificate of Incorporation and Bylaws

In addition to the board of directors' ability to issue shares of preferred stock, our restated certificate of incorporation and restated bylaws contain other provisions that are intended to enhance the likelihood of continuity and stability in the composition of the board of directors and which may have the effect of delaying, deferring or preventing a future takeover or change in control of our company unless such takeover or change in control is approved by our board of directors.

These provisions, summarized below, are expected to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to encourage persons seeking to acquire control of us to first negotiate with our board of directors. We believe that the benefits of increased protection of our potential ability to negotiate with the proponent of an unfriendly or unsolicited proposal to acquire or restructure us outweigh the disadvantages of discouraging these proposals because negotiation of these proposals could result in an improvement of their terms.

Classified board of directors; removal of directors for cause. Our restated certificate of incorporation and restated bylaws provide for our board of directors to be divided into three classes serving staggered terms. At each annual meeting of stockholders, directors elected to succeed those directors whose terms have expired are elected for a three-year term of office. All directors elected to our classified board of directors will serve until the election and qualification of their respective successors or their earlier resignation or removal. The board of directors is authorized to create new directorships and to fill such positions so created and is permitted to specify the class to which any such new position is assigned. The person filling such position would serve for the term applicable to that class. The board of directors (or its remaining members, even if less than a quorum) is also empowered to fill vacancies on the board of directors occurring for any reason for the remainder of the term of the class of directors in which the vacancy occurred. Members of the board of directors may only be removed for cause and only by the affirmative vote of 80% of our outstanding voting stock. These provisions are likely to increase the time required for stockholders to change the composition of the board of directors. For example, in general, at least two annual meetings will be necessary for stockholders to effect a change in a majority of the members of the board of directors. The provision for a classified board could prevent a party who acquires control of a majority of our outstanding common stock from obtaining control of our board of directors until our second annual stockholders meeting following the date the acquirer obtains the controlling stock interest. The classified board provision could have the effect of discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of us and could increase the likelihood that incumbent directors will retain their positions.

Advance notice provisions for stockholder proposals. Our restated bylaws establish an advance notice procedure for stockholder proposals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors, as well as procedures for including proposed nominations at special meetings at which directors are to be elected. Stockholders at our annual meeting may only consider proposals or nominations specified in the notice of meeting or brought before the meeting by or at the direction of our board or by a stockholder who was a stockholder of record on the record date for the meeting, who is entitled to vote at the meeting and who has given to our secretary timely written notice, in proper form, of the stockholder's intention to bring that business before the meeting, and who has complied with the procedures and requirements set forth in the bylaws. Although our bylaws do not give our board of directors the power to approve or disapprove stockholder nominations of candidates or proposals regarding other business to be conducted at a special or annual meeting, our bylaws may have the effect of precluding the conduct of some business at a meeting if the proper procedures are not followed or may discourage or defer a potential acquirer from conducting a solicitation of proxies to elect its own slate of directors or otherwise attempting to obtain control of us.

Special meetings of stockholders. Special meetings of the stockholders may be called only by our board of directors pursuant to a resolution adopted by a majority of the total number of authorized directors. Stockholders are not permitted to call a special meeting or to require our board of directors to call a special meeting.

No stockholder action by written consent. Our restated certificate of incorporation and restated bylaws do not permit our stockholders to act by written consent. As a result, any action to be effected by our stockholders must be effected at a duly called annual or special meeting of the stockholders.

Super-majority stockholder vote required for certain actions. The Delaware General Corporation Law, or DGCL, provides generally that the affirmative vote of a majority of the shares entitled to vote on any matter is required to amend a corporation's certificate of incorporation or bylaws, unless the corporation's certificate of incorporation or bylaws, as the case may be, requires a greater percentage. Our restated certificate of incorporation requires the affirmative vote of the holders of at least 80% of our outstanding voting stock to amend or repeal certain provisions of our restated certificate of incorporation. This 80% stockholder vote would be in addition to any separate class vote that might in the future be required pursuant to the terms of any preferred stock that might then be outstanding. In addition, an 80% vote is also required for any amendment to, or repeal of, our restated bylaws by the stockholders. Our restated bylaws may be amended or repealed by a vote of a majority of the total number of authorized directors.

Provisions of Delaware Law Governing Business Combinations

We are subject to the "business combination" provisions of Section 203 of the DGCL. In general, such provisions prohibit a publicly held Delaware corporation from engaging in any "business combination" transactions with any "interested stockholder" for a period of three years after the date on which the person became an "interested stockholder," unless:

- prior to such date, the board of directors approved either the "business combination" or the transaction which resulted in the "interested stockholder" obtaining such status; or

- upon consummation of the transaction which resulted in the stockholder becoming an "interested stockholder," the "interested stockholder" owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the voting stock outstanding (but not the outstanding voting stock owned by the "interested stockholder") those shares owned by (a) persons who are directors and also officers and (b) employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or

- at or subsequent to such time the "business combination" is approved by the board of directors and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least $66^{2}/_{3}\%$ of the outstanding voting stock which is not owned by the "interested stockholder."

A "business combination" is defined to include mergers, asset sales and other transactions resulting in financial benefit to a stockholder. In general, an "interested stockholder" is a person who, together with affiliates and associates, owns 15% or more of a corporation's voting stock or within three years did own 15% or more of a corporation's voting stock. The statute could prohibit or delay mergers or other takeover or change in control attempts with respect to us and, accordingly, may discourage attempts to acquire us.

SELLING STOCKHOLDERS

On July 22, 2016, Synta Pharmaceuticals Corp., or Synta, completed its business combination with Madrigal Pharmaceuticals, Inc., a privately-held Delaware corporation, or Private Madrigal, in accordance with the terms of an Agreement and Plan of Merger and Reorganization, dated as of April 13, 2016, or the Merger Agreement, whereby a wholly-owned subsidiary of Synta merged with and into Private Madrigal, or the Merger, with Private Madrigal surviving the Merger as a wholly-owned subsidiary of Synta. Under the terms of the Merger Agreement, at the effective time of the Merger, we issued an aggregate of 7,253,655 shares of common stock to the stockholders of Private Madrigal, in exchange for each share of common stock of Private Madrigal outstanding immediately prior to the Merger. In connection with the Merger, we agreed to file with the SEC a registration statement on Form S-3 to register the shares of common stock issued to the former stockholders of Private Madrigal in the Merger.

This prospectus supplement relates in part to the offering by the selling stockholders of up to 363,625 shares of our common stock consisting of an aggregate of 353,526 shares of our common stock issued to the selling stockholders upon consummation of the Merger pursuant to the terms of the Merger Agreement and an aggregate of 10,099 shares of our common stock subject to restricted stock awards and stock options held by a selling stockholder. The following table sets forth, based on information provided to us by the selling stockholders or known to us, the name of the selling stockholders and the number of shares of our common stock beneficially owned by the selling stockholders before this offering. The number of shares owned are those beneficially owned, as determined under the rules of the SEC, and the information is not necessarily indicative of beneficial ownership for any other purpose. Under these rules, beneficial ownership includes any shares of common stock as to which a person has sole or shared voting power or investment power and any shares of common stock which the person has the right to acquire within 60 days through the exercise of any option, warrant or right, through conversion of any security or pursuant to the automatic termination of a power of attorney or revocation of a trust, discretionary account or similar arrangement.

We have assumed all shares of common stock reflected on the table will be sold from time to time in the offering covered by this prospectus supplement. Because the selling stockholders may offer all or any portions of the shares of common stock listed in the table below, no estimate can be given as to the amount of those shares of common stock covered by this prospectus supplement that will be held by the selling stockholders upon the termination of the offering. The percent of shares beneficially owned by our selling stockholders prior to the offering is based on 14,250,726 shares of our common stock outstanding on May 31, 2018. The percent of shares beneficially owned by the selling stockholders after the offering assumes the sale by us of $200 million of shares of our common stock in the offering at an assumed public offering price of $273.24 per share (the last reported sale price on the The Nasdaq Global Market on June 4, 2018).

	Shares Beneficially Owned Prior to Offering		Number of Shares to be Sold	Shares Beneficially Owned After Offering	
Name of Selling Stockholder	Shares	Percentage		Shares	Percentage
Entities Affiliated with Bay City Capital, LLC[1]	5,657,854	39.7%	280,000	5,377,854	35.9%
SQN, LLC[2]	729,066	5.1%	73,526	655,540	4.4%
Marc R. Schneebaum[3]	92,535	*	10,099	82,436	*

* Less than one percent

(1) Consists of 5,538,474 shares of common stock issued to Bay City Capital Fund IV, L.P., or Fund IV, upon consummation of the Merger, and 119,380 shares of common stock issued to

Bay City Capital Fund IV Co-Investment Fund, L.P., or Co-Invest Fund, upon consummation of the Merger. Fund IV and Co-Invest Fund were stockholders and holders of convertible debt of Private Madrigal prior to the consummation of the Merger. Bay City Capital Management IV LLC, or BCC IV, is the general partner of Fund IV and Co-Invest Fund and has sole voting and investment power over the shares held by Fund IV and Co-Invest Fund. Bay City Capital, LLC, or BCC, is the manager of BCC IV, and thus has sole voting and investment power over the shares held by Fund IV and Co-Invest Fund. Fred B. Craves, Ph.D. is a managing director of BCC and thus may be deemed to share voting and investment power over the shares beneficially owned by these entities. The address for the entities affiliated with BCC is 750 Battery Street, Suite 400, San Francisco, California 94111.

(2) Consists of 729,066 shares of common stock issued to SQN, LLC upon consummation of the Merger. SQN, LLC held convertible debt of Private Madrigal prior to the consummation of the Merger. Paul A. Friedman, M.D. and Rebecca Taub, M.D. are the managing members of SQN, LLC and thus may be deemed to share voting and investment power over the shares beneficially owned by SQN, LLC. Dr. Friedman and Dr. Taub disclaim beneficial ownership of the shares beneficially owned by SQN, LLC except to the extent of their pecuniary interest therein. The address for SQN, LLC is c/o Madrigal Pharmaceuticals, Inc., 200 Barr Harbor Drive, Suite 400, West Conshohocken, Pennsylvania 19428.

(3) Consists of 65,891 shares of common stock issuable upon the exercise of options exercisable within sixty days of May 31, 2018, and 26,644 shares of restricted common stock (of which 12,250 shares vest within sixty days of May 31, 2018). Mr. Schneebaum currently serves as our Chief Financial Officer.

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

The following discussion is a summary of the material U.S. federal income tax consequences to non-U.S. holders (as defined below) of the purchase, ownership and disposition of the shares of common stock issued pursuant to this offering, but does not purport to be a complete analysis of all potential tax effects. The effects of other U.S. federal tax laws, such as estate and gift tax laws, and any applicable state, local or foreign tax laws are not discussed. This discussion is based on the Internal Revenue Code of 1986, as amended, or the Code, Treasury Regulations promulgated thereunder, judicial decisions, and published rulings and administrative pronouncements of the U.S. Internal Revenue Service, or IRS, in effect as of the date of this offering. These authorities may change or be subject to differing interpretations. Any such change or differing interpretation may be applied retroactively in a manner that could adversely affect a non-U.S. holder of our common stock. We have not sought and will not seek any rulings from the IRS regarding the matters discussed below. There can be no assurance the IRS or a court will not take a contrary position regarding the tax consequences of the purchase, ownership and disposition of our common stock.

This discussion is limited to non-U.S. holders that hold our common stock as a "capital asset" within the meaning of Section 1221 of the Code (property held for investment). This discussion does not address all U.S. federal income tax consequences relevant to a non-U.S. holder's particular circumstances, including the impact of the alternative minimum tax or the unearned income Medicare contribution tax. In addition, it does not address consequences relevant to holders subject to particular rules, including, without limitation:

- U.S. expatriates and certain former citizens or long-term residents of the United States;
- persons holding our common stock as part of a hedge, straddle or other risk reduction strategy or as part of a conversion transaction or other integrated investment;
- banks, insurance companies, and other financial institutions;
- brokers, dealers or traders in securities or currencies;
- "controlled foreign corporations," "passive foreign investment companies," and corporations that accumulate earnings to avoid U.S. federal income tax;
- partnerships or other entities or arrangements treated as partnerships for U.S. federal income tax purposes (and investors therein);
- tax-exempt organizations or governmental organizations;
- persons deemed to sell our common stock under the constructive sale provisions of the Code;
- persons for whom our common stock constitutes "qualified small business stock" within the meaning of Section 1202 of the Code;
- persons subject to special tax accounting rules as a result of any item of gross income with respect to our common stock being taken into account in an "applicable financial statement" (as defined in the Code);
- persons who hold or receive our common stock pursuant to the exercise of any employee stock option or otherwise as compensation; and
- tax-qualified retirement plans.

If a partnership (or other entity treated as a partnership for U.S. federal income tax purposes) holds our common stock, the tax treatment of a partner in the partnership will depend on the status of the partner, the activities of the partnership and certain determinations made at the partner level.

Accordingly, partnerships holding our common stock and the partners in such partnerships should consult their tax advisors regarding the U.S. federal income tax consequences to them.

THIS DISCUSSION IS FOR INFORMATION PURPOSES ONLY AND IS NOT INTENDED AS LEGAL OR TAX ADVICE. INVESTORS SHOULD CONSULT THEIR TAX ADVISORS WITH RESPECT TO THE APPLICATION OF THE U.S. FEDERAL INCOME TAX LAWS TO THEIR PARTICULAR SITUATIONS AS WELL AS ANY TAX CONSEQUENCES OF THE PURCHASE, OWNERSHIP AND DISPOSITION OF OUR COMMON STOCK ARISING UNDER THE U.S. FEDERAL ESTATE OR GIFT TAX LAWS OR UNDER THE LAWS OF ANY STATE, LOCAL OR NON-U.S. TAXING JURISDICTION OR UNDER ANY APPLICABLE INCOME TAX TREATY.

Definition of a Non-U.S. Holder

For purposes of this discussion, a "non-U.S. holder" is any beneficial owner of our common stock that is not a "U.S. person," a partnership or an entity disregarded as separate from its owner, each for United States federal income tax purposes. A U.S. person is any person that, for U.S. federal income tax purposes, is:

- an individual who is a citizen or resident of the United States;
- a corporation (or other entity treated as a corporation for U.S. federal income tax purposes) created or organized under the laws of the United States, any state thereof, or the District of Columbia;
- an estate, the income of which is subject to U.S. federal income tax regardless of its source; or
- a trust that (1) is subject to the primary supervision of a U.S. court and the control of one or more United States persons (within the meaning of Section 7701(a)(30) of the Code), or (2) has made a valid election under applicable Treasury Regulations to continue to be treated as a United States person.

Distributions

As described in the section entitled "Dividend Policy," we do not anticipate paying dividends to holders of our common stock in the foreseeable future. However, if we do make distributions on our common stock, such distributions of cash or property on our common stock will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. Amounts not treated as dividends for U.S. federal income tax purposes will constitute a return of capital and first be applied against and reduce a non-U.S. holder's adjusted tax basis in its common stock, but not below zero. Any excess will be treated as capital gain and will be treated as described below in the section relating to the sale or disposition of our common stock. Because we may not know the extent to which a distribution is a dividend for U.S. federal income tax purposes at the time it is made, for purposes of the withholding rules discussed below we or the applicable withholding agent may treat the entire distribution as a dividend.

Subject to the discussion below on backup withholding and foreign accounts, dividends paid to a non-U.S. holder of our common stock that are not effectively connected with the non-U.S. holder's conduct of a trade or business within the United States will be subject to U.S. federal withholding tax at a rate of 30% of the gross amount of the dividends (or such lower rate specified by an applicable income tax treaty).

Non-U.S. holders will be entitled to a reduction in or an exemption from withholding on dividends as a result of either (a) an applicable income tax treaty or (b) the non-U.S. holder holding

our common stock in connection with the conduct of a trade or business within the United States and dividends being effectively connected with that trade or business. To claim such a reduction in or exemption from withholding, the non-U.S. holder must provide the applicable withholding agent with a properly executed (a) IRS Form W-8BEN or W-8BEN-E (or other applicable documentation) claiming an exemption from or reduction of the withholding tax under the benefit of an income tax treaty between the United States and the country in which the non-U.S. holder resides or is established, or (b) IRS Form W-8ECI stating that the dividends are not subject to withholding tax because they are effectively connected with the conduct by the non-U.S. holder of a trade or business within the United States, as may be applicable. These certifications must be provided to the applicable withholding agent prior to the payment of dividends and must be updated periodically. Non-U.S. holders that do not timely provide the applicable withholding agent with the required certification, but that qualify for a reduced rate under an applicable income tax treaty, may obtain a refund of any excess amounts withheld by timely filing an appropriate claim for refund with the IRS.

If dividends paid to a non-U.S. holder are effectively connected with the non-U.S. holder's conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, the non-U.S. holder maintains a permanent establishment in the United States to which such dividends are attributable), then, although exempt from U.S. federal withholding tax (provided the non-U.S. holder provides appropriate certification, as described above), the non-U.S. holder will be subject to U.S. federal income tax on such dividends on a net income basis at the regular graduated U.S. federal income tax rates. In addition, a non-U.S. holder that is a corporation may be subject to a branch profits tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on its effectively connected earnings and profits for the taxable year that are attributable to such dividends, as adjusted for certain items. Non-U.S. holders should consult their tax advisors regarding their entitlement to benefits under any applicable income tax treaty.

Sale or Other Disposition of Common Stock

Subject to the discussions below on backup withholding and foreign accounts, a non-U.S. holder will not be subject to U.S. federal income tax on any gain realized upon the sale or other disposition of our common stock unless:

- the gain is effectively connected with the non-U.S. holder's conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, the non-U.S. holder maintains a permanent establishment in the United States to which such gain is attributable);
- the non-U.S. holder is a nonresident alien individual present in the United States for 183 days or more during the taxable year of the disposition and certain other requirements are met; or
- our common stock constitutes U.S. real property interests, or USRPIs, by reason of our status as a U.S. real property holding corporation, or USRPHC, for U.S. federal income tax purposes.

Gain described in the first bullet point above will generally be subject to U.S. federal income tax on a net income basis at the regular graduated U.S. federal income tax rates. A non-U.S. holder that is a foreign corporation also may be subject to a branch profits tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on such effectively connected gain, as adjusted for certain items.

A non-U.S. holder described in the second bullet point above will be subject to U.S. federal income tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on

any gain derived from the disposition, which may be offset by certain U.S. source capital losses of the non-U.S. holder (even though the individual is not considered a resident of the United States) provided the non-U.S. holder has timely filed U.S. federal income tax returns with respect to such losses.

With respect to the third bullet point above, we believe we are not currently and do not anticipate becoming a USRPHC. Because the determination of whether we are a USRPHC depends on the fair market value of our USRPIs relative to the fair market value of our other business assets and our non-U.S. real property interests, however, there can be no assurance we are not a USRPHC or will not become one in the future. Even if we are or were to become a USRPHC, gain arising from the sale or other taxable disposition by a non-U.S. holder of our common stock will not be subject to U.S. federal income tax if our common stock is "regularly traded," as defined by applicable Treasury Regulations, on an established securities market, and such non-U.S. holder owned, actually and constructively, 5% or less of our common stock throughout the shorter of the five-year period ending on the date of the sale or other taxable disposition or the non-U.S. holder's holding period. If we are a USRPHC and either our common stock is not regularly traded on an established securities market or a non-U.S. holder holds more than 5% of our outstanding common stock, directly or indirectly, during the applicable testing period, such non-U.S. holder's gain on the disposition of shares of our common stock generally will be taxed in the same manner as gain that is effectively connected with the conduct of a U.S. trade or business, except that the branch profits tax generally will not apply. If we are a USRPHC and our common stock is not regularly traded on an established securities market, a non-U.S. holder's proceeds received on the disposition of our common stock will also generally be subject to withholding at a rate of 15%. Prospective investors are encouraged to consult their tax advisors regarding the possible consequences to them if we are, or were to become, a USRPHC.

Non-U.S. holders should consult their tax advisors regarding potentially applicable income tax treaties that may provide for different rules.

Information Reporting and Backup Withholding

Subject to the discussion below on foreign accounts, a non-U.S. holder will not be subject to backup withholding with respect to distributions on our common stock we make to the non-U.S. holder, provided the applicable withholding agent does not have actual knowledge or reason to know such holder is a United States person and the holder certifies its non-U.S. status, such as by providing a valid IRS Form W-8BEN, W-8BEN-E or W-8ECI, or other applicable certification. However, information returns generally will be filed with the IRS in connection with any distributions (including deemed distributions) made on our common stock to the non-U.S. holder, regardless of whether any tax was actually withheld. Copies of these information returns may also be made available under the provisions of a specific treaty or agreement to the tax authorities of the country in which the non-U.S. holder resides or is established.

Information reporting and backup withholding may apply to the proceeds of a sale or other taxable disposition of our common stock within the United States, and information reporting may (although backup withholding generally will not) apply to the proceeds of a sale or other taxable disposition of our common stock outside the United States conducted through certain U.S.-related financial intermediaries, in each case, unless the beneficial owner certifies under penalty of perjury that it is a non-U.S. holder on IRS Form W-8BEN or W-8BEN-E, or other applicable form (and the payor does not have actual knowledge or reason to know that the beneficial owner is a U.S. person) or such owner otherwise establishes an exemption. Proceeds of a disposition of our common stock conducted through a non-U.S. office of a non-U.S. broker generally will not be subject to backup withholding or information reporting.

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

Additional Withholding Tax on Payments Made to Foreign Accounts

Withholding taxes may be imposed under the Foreign Account Tax Compliance Act, or FATCA, on certain types of payments made to non-U.S. financial institutions and certain other non-U.S. entities. Specifically, a 30% withholding tax may be imposed on dividends (including deemed dividends) paid on our common stock, or gross proceeds from the sale or other disposition of our common stock paid to a "foreign financial institution" or a "non-financial foreign entity" (each as defined in the Code), unless (1) the foreign financial institution undertakes certain diligence and reporting obligations, (2) the non-financial foreign entity either certifies it does not have any "substantial United States owners" (as defined in the Code) or furnishes identifying information regarding each substantial United States owner, or (3) the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from these rules. If the payee is a foreign financial institution and is subject to the diligence and reporting requirements in (1) above, it must enter into an agreement with the U.S. Department of the Treasury requiring, among other things, that it undertake to identify accounts held by certain "specified United States persons" or "United States-owned foreign entities" (each as defined in the Code), annually report certain information about such accounts, and withhold 30% on certain payments to non-compliant foreign financial institutions and certain other account holders. Foreign financial institutions located in jurisdictions that have an intergovernmental agreement with the United States governing FATCA may be subject to different rules.

Under the applicable Treasury Regulations and administrative guidance, withholding under FATCA generally applies to payments of dividends (including deemed dividends) paid on our common stock, and will apply to payments of gross proceeds from the sale or other disposition of our common stock on or after January 1, 2019. Because we may not know the extent to which a distribution is a dividend for U.S. federal income tax purposes at the time it is made, for purposes of these withholding rules we or the applicable withholding agent may treat the entire distribution as a dividend. Prospective investors should consult their tax advisors regarding the potential application of these withholding provisions.

UNDERWRITING

The company, the selling stockholders and Goldman Sachs & Co. LLC have entered into an underwriting agreement with respect to the shares being offered. Subject to certain conditions, Goldman Sachs & Co. LLC has agreed to purchase the number of shares indicated in the following table.

Underwriter	Number of Shares
Goldman Sachs & Co. LLC	

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

The underwriter has an option to buy additional shares from us up to an aggregate amount of 15% of the base deal shares. The underwriter may exercise that option for 30 days.

The following tables show the per share and total underwriting discounts and commissions to be paid to the underwriter by the company and the selling stockholders. In the case of the company, such amounts are shown assuming both no exercise and full exercise of the underwriter's option to purchase additional shares from the Company.

Paid by the Company

	No Exercise	Full Exercise
Per Share	$	$
Total	$	$

Paid by the Selling Stockholders

	No Exercise	Full Exercise
Per Share	$	$
Total	$	$

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

The company, its officers, directors, certain existing stockholders and the selling stockholders have agreed with the underwriter, subject to certain exceptions, not to dispose of or hedge any of their common stock or securities convertible into or exchangeable for shares of common stock during the period from the date of this prospectus supplement continuing through the date 90 days after the date of this prospectus supplement, except with the prior written consent of Goldman Sachs & Co. LLC. This agreement does not apply to any existing employee benefit plans.

Our common stock is listed on The Nasdaq Global Market under the symbol "MDGL".

In connection with the offering, the underwriter may purchase and sell shares of common stock in the open market. These transactions may include short sales, stabilizing transactions and purchases to cover positions created by short sales. Short sales involve the sale by the underwriter of a greater number of shares than they are required to purchase in the offering, and a short

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

Purchases to cover a short position and stabilizing transactions, as well as other purchases by the underwriter for its own account, may have the effect of preventing or retarding a decline in the market price of the company's stock, and may stabilize, maintain or otherwise affect the market price of the common stock. As a result, the price of the common stock may be higher than the price that otherwise might exist in the open market. The underwriter is not required to engage in these activities and may end any of these activities at any time. These transactions may be effected on the Nasdaq Global Market, in the over-the-counter market or otherwise.

The company and the selling stockholders estimate that their share of the total expenses of the offering, excluding underwriting discounts and commissions, will be approximately $. The underwriters have agreed to reimburse the Company for certain expenses in connection with the offering.

The company and the selling stockholders have agreed to indemnify the underwriter against certain liabilities, including liabilities under the Securities Act of 1933, as amended.

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

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

Selling Restrictions

European Economic Area

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

- to any legal entity which is a qualified investor as defined in the Prospectus Directive;
- to fewer than 150 natural or legal persons (other than qualified investors as defined in the Prospectus Directive) subject to obtaining the prior consent of the representative for any such offer; or
- in any other circumstances falling within Article 3(2) of the Prospectus Directive;
- provided that no such offer of shares of our common stock shall result in a requirement for the publication by us or any Brazilian placement agent of a prospectus pursuant to Article 3 of the Prospectus Directive.

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

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

United Kingdom

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

Canada

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

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

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

Hong Kong

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

Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the shares may not be circulated or distributed, nor may the shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor (as defined under Section 4A of the Securities and Futures Act, Chapter 289 of Singapore (the "SFA")) under Section 274 of the SFA, (ii) to a relevant person (as defined in Section 275(2) of the SFA) pursuant to Section 275(1) of the SFA, or any person pursuant to Section 275(1A) of the SFA, and in accordance with the conditions specified in Section 275 of the SFA or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA, in each case subject to conditions set forth in the SFA. Where the shares are subscribed or purchased under Section 275 of the SFA by a relevant person which is a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor, the securities (as defined in Section 239(1) of the SFA) of that corporation shall not be transferable for 6 months after that corporation has acquired the shares under Section 275 of the SFA except: (1) to an institutional investor under Section 274 of the SFA or to a relevant person (as defined in Section 275(2) of the SFA), (2) where such transfer arises from an offer in that corporation's securities pursuant to Section 275(1A) of the

SFA, (3) where no consideration is or will be given for the transfer, (4) where the transfer is by operation of law, (5) as specified in Section 276(7) of the SFA, or (6) as specified in Regulation 32 of the Securities and Futures (Offers of Investments) (Shares and Debentures) Regulations 2005 of Singapore ("Regulation 32").

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

Japan

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

LEGAL MATTERS

Certain legal matters will be passed upon for us by Baker & Hostetler, LLP, Costa Mesa, California. Certain legal matters will be passed upon for the underwriter by Ropes & Gray LLP, Boston, Massachusetts.

EXPERTS

The financial statements and management's assessment of the effectiveness of internal control over financial reporting (which is included in Management's Report on Internal Control over Financial Reporting) incorporated in this prospectus supplement by reference to the Annual Report on Form 10-K for the year ended December 31, 2017 have been so incorporated in reliance on the report of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus supplement and the accompanying prospectus are part of a registration statement on Form S-3 that we filed with the SEC registering the securities that may be offered and sold hereunder. The registration statement, including exhibits thereto, contains additional relevant information about us and these securities that, as permitted by the rules and regulations of the SEC, we have not included in this prospectus supplement or the accompanying prospectus. A copy of the registration statement can be obtained at the address set forth below. You should read the registration statement for further information about us and these securities.

We file annual, quarterly and special reports, proxy statements and other information with the SEC under the Exchange Act. You may read and copy this information at the following SEC location:

Public Reference Room
100 F Street, N.E.
Washington, D.C. 20549

You may obtain information on the operation of the Public Reference Room by calling the SEC at (800) SEC-0330. The SEC also maintains a web site that contains reports, proxy statements, information statements and other information about issuers, like Madrigal Pharmaceuticals, Inc., who file electronically with the SEC. The address of that web site is www.sec.gov.

In addition, our common stock is listed on The Nasdaq Global Market and similar information concerning us can be inspected and copied at the offices of The Nasdaq Stock Market, One Liberty Plaza, 165 Broadway, New York, NY 10006.

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

This prospectus supplement and the accompanying prospectus are part of a registration statement on Form S-3 filed by us with the SEC. This prospectus supplement and the accompanying prospectus do not contain all of the information set forth in the registration statement, certain parts of which are omitted in accordance with the rules and regulations of the SEC. For further information about us and the securities offered by this prospectus supplement and the accompanying prospectus, we refer you to the registration statement and its exhibits and schedules which may be obtained as described herein.

The SEC allows us to "incorporate by reference" information into this prospectus supplement and the accompanying prospectus. This means that we can disclose important information about us and our financial condition to you by referring you to another document filed separately with the SEC. The information incorporated by reference is considered to be part of this prospectus

supplement and the accompanying prospectus. This prospectus supplement and the accompanying prospectus incorporate by reference the documents listed below that we have previously filed with the SEC:

- our Annual Report on Form 10-K for the fiscal year ended December 31, 2017, as filed with the SEC on March 13, 2018;
- our Definitive Proxy Statement on Schedule 14A, as filed with the SEC on April 27, 2018;
- our Quarterly Report on Form 10-Q for the fiscal quarter ended March 31, 2018, as filed with the SEC on May 8, 2018;
- our Current Report on Form 8-K, as filed with the SEC on May 31, 2018; and
- the description of our common stock contained in our Registration Statement on Form 8-A, filed with the SEC on January 26, 2007, including any amendment or report filed for the purpose of updating such description.

We also incorporate by reference into this prospectus supplement and the accompanying prospectus all documents filed by us with the SEC pursuant to Sections 12(a), 13(c), 14 or 15(d) of the Exchange Act prior to the termination of any offering of securities made by this prospectus supplement and the accompanying prospectus. Nothing in this prospectus supplement or the accompanying prospectus shall be deemed to incorporate information furnished but not filed with the SEC (including without limitation, information furnished under Item 2.02 or Item 7.01 of Form 8-K, and any exhibits relating to such information).

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

You may request a copy of the filings incorporated herein by reference, including exhibits to such documents that are specifically incorporated by reference, at no cost, by writing or calling us at the following address or telephone number:

Marc R. Schneebaum
Chief Financial Officer
Madrigal Pharmaceuticals, Inc.
Four Tower Bridge
200 Barr Harbor Drive, Suite 400
West Conshohocken, Pennsylvania 19428
(484) 380-9263

Statements contained in this prospectus supplement and the accompanying prospectus as to the contents of any contract or other documents are not necessarily complete, and in each instance investors are referred to the copy of the contract or other document filed as an exhibit to the registration statement, each such statement being qualified in all respects by such reference and the exhibits and schedules thereto.

Table of Contents

PROSPECTUS

Madrigal Pharmaceuticals, Inc.

Common Stock

Preferred Stock

Warrants

Units

Debt Securities

By this prospectus, we or any selling stockholder may offer and sell from time to time, in one or more offerings, common stock, preferred stock, warrants, debt securities or any combination thereof as described in this prospectus. The warrants may be convertible into or exercisable or exchangeable for common stock or preferred stock, the preferred stock may be convertible into or exchangeable for common stock and the debt securities may be convertible into or exchangeable for common stock or preferred stock. You should carefully read this prospectus, any prospectus supplement and any free writing prospectus, as well as any documents incorporated in any of the foregoing by reference, before you invest in our securities. This prospectus may not be used to sell our securities unless accompanied by a prospectus supplement. The prospectus supplement or any related free writing prospectus may also add to, update, supplement or clarify information contained in this prospectus.

Our common stock is traded on the NASDAQ Global Market under the symbol "MDGL."

We or any selling stockholder may offer and sell our securities to or through one or more agents, underwriters, dealers or other third parties or directly to one or more purchasers on a continuous or delayed basis. If agents, underwriters or dealers are used to sell our securities, we or any selling stockholder will name them and describe their compensation in a prospectus supplement. The price to the public of our securities and the net proceeds we expect to receive from the sale of such securities will also be set forth in a prospectus supplement. We will not receive any proceeds from the sale of securities by selling stockholders.

INVESTING IN OUR SECURITIES INVOLVES A HIGH DEGREE OF RISK. YOU SHOULD REVIEW CAREFULLY THE RISKS AND UNCERTAINTIES REFERENCED UNDER THE HEADING "*RISK FACTORS*" ON PAGE 5 OF THIS PROSPECTUS AS WELL AS THOSE CONTAINED IN THE APPLICABLE PROSPECTUS SUPPLEMENT AND ANY RELATED FREE WRITING PROSPECTUS, AND IN THE OTHER DOCUMENTS THAT ARE INCORPORATED BY REFERENCE INTO THIS PROSPECTUS OR THE APPLICABLE PROSPECTUS SUPPLEMENT.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus is June 5, 2018.

TABLE OF CONTENTS

We are responsible for the information contained and incorporated by reference in this prospectus, in any accompanying prospectus supplement, and in any related free writing prospectus we prepare or authorize. We have not authorized anyone to give you any other information, and we take no responsibility for any other information that others may give you. If you are in a jurisdiction where offers to sell, or solicitations of offers to purchase, the securities offered by this documentation are unlawful, or if you are a person to whom it is unlawful to direct these types of activities, then the offer presented in this document does not extend to you. The information contained in this document speaks only as of the date of this document, unless the information specifically indicates that another date applies. Our business, financial condition, results of operations and prospectus may have changed since those dates.

ABOUT THIS PROSPECTUS

This prospectus is part of an automatic shelf registration statement that we filed with the Securities and Exchange Commission, or the SEC, as a "well-known seasoned issuer" as defined in Rule 405 under the Securities Act of 1933, as amended, or the Securities Act. Under this shelf registration, we and/or selling stockholders may offer shares of our common stock and preferred stock, various series of warrants to purchase common stock or preferred stock, debt securities or any combination thereof, from time to time in one or more offerings. This prospectus only provides you with a general description of the securities we and/or selling stockholders may offer. Each time we and/or selling stockholders offer a type or series of securities under this prospectus, we will provide a prospectus supplement that will contain more specific information about the specific terms of the offering. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. This prospectus may not be used to sell our securities unless accompanied by a prospectus supplement. Each such prospectus supplement and any free writing prospectus that we may authorize to be provided to you may also add, update or change information contained in this prospectus or in documents incorporated by reference into this prospectus. We urge you to carefully read this prospectus, any applicable prospectus supplement and any related free writing prospectus, together with the information incorporated herein by reference as described under the headings "Where You Can Find Additional Information" and "Incorporation of Certain Information by Reference" before you invest in our securities.

Neither we nor any selling stockholder have authorized anyone to provide you with information in addition to or different from that contained in this prospectus, any applicable prospectus supplement and any related free writing prospectus. We take no responsibility for, and can provide no assurances as to the reliability of, any information not contained in this prospectus, any applicable prospectus supplement or any related free writing prospectus that we or a selling stockholder may authorize to be provided to you. This prospectus is an offer to sell only the securities offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. You should assume that the information in this prospectus, any applicable prospectus supplement or any related free writing prospectus is accurate only as of the date on the front of the document and that any information incorporated by reference is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of this prospectus, any applicable prospectus supplement or any related free writing prospectus, or any sale of a security.

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

Unless otherwise mentioned or unless the context requires otherwise, throughout this prospectus, any applicable prospectus supplement and any related free writing prospectus, the words "Madrigal," "we," "us," "our," the "company" or similar references refer to Madrigal Pharmaceuticals, Inc. and its subsidiaries; and the term "securities" refers collectively to our common stock, preferred stock, warrants to purchase common stock or preferred stock, debt securities, or any combination of the foregoing securities.

This prospectus and the information incorporated herein by reference contains references to trademarks, service marks and trade names owned by us or other companies. Solely for convenience, trademarks, service marks and trade names referred to in this prospectus and the information incorporated herein, including logos, artwork, and other visual displays, may appear without the ® or ^{TM} symbols, but such references are not intended to indicate, in any way, that we will not assert, to

the fullest extent under applicable law, our rights or the rights of the applicable licensor to these trademarks, service marks and trade names. We do not intend our use or display of other companies' trade names, service marks or trademarks to imply a relationship with, or endorsement or sponsorship of us by, any other companies. All trademarks, service marks and trade names included or incorporated by reference into this prospectus, any applicable prospectus supplement or any related free writing prospectus are the property of their respective owners.

WHERE YOU CAN FIND ADDITIONAL INFORMATION

This prospectus is part of a registration statement that we have filed with the SEC. Certain information in the registration statement has been omitted from this prospectus in accordance with the rules of the SEC. We are subject to the information requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act, and, in accordance therewith, file annual, quarterly and special reports, proxy statements and other information with the SEC. You may read and copy any document we file at the SEC's Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549. You may call the SEC at 1-800-SEC-0330 for further information on the operation of the Public Reference Room. These documents also may be accessed through the SEC's Electronic Data Gathering, Analysis and Retrieval system, or EDGAR, via electronic means, including the SEC's home page on the Internet (*www.sec.gov*).

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to incorporate by reference much of the information we file with the SEC, which means that we can disclose important information to you by referring you to those publicly available documents. The information that we incorporate by reference in this prospectus is considered to be part of this prospectus. Because we are incorporating by reference future filings with the SEC, this prospectus supplement is continually updated and those future filings may modify or supersede some of the information included or incorporated in this prospectus. This means that you must look at all of the SEC filings that we incorporate by reference to determine if any of the statements in this prospectus or in any document previously incorporated by reference have been modified or superseded. This prospectus incorporates by reference the documents listed below and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act (in each case, other than those documents or the portions of those documents not deemed to be filed) between the date of this prospectus and the termination of this offering:

- our Annual Report on Form 10-K for the fiscal year ended December 31, 2017, as filed with the SEC on March 13, 2018;
- our Definitive Proxy Statement on Schedule 14A, as filed with the SEC on April 27, 2018;
- our Quarterly Report on Form 10-Q for the fiscal quarter ended March 31, 2018, as filed with the SEC on May 8, 2018;
- our Current Report on Form 8-K, as filed with the SEC on May 31, 2018; and
- the description of our common stock contained in our Registration Statement on Form 8-A, filed with the SEC on January 26, 2007, including any amendment or report filed for the purpose of updating such description.

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

Marc R. Schneebaum
Chief Financial Officer
Madrigal Pharmaceuticals, Inc.
Four Tower Bridge
200 Barr Harbor Drive, Suite 400
West Conshohocken, Pennsylvania 19428
(484) 380-9263

You may also access these documents, free of charge on the SEC's website at *www.sec.gov* or on our website at *www.madrigalpharma.com*. The information contained in, or that can be accessed through, our website is not part of this prospectus.

This prospectus is part of a registration statement we filed with the SEC. We have incorporated exhibits into this registration statement. You should read the exhibits carefully for provisions that may be important to you.

Neither we nor any selling stockholder have authorized anyone to provide you with information other than what is incorporated by reference or provided in this prospectus or any prospectus supplement. Neither we nor any selling stockholder are making an offer of these securities in any state where the offer is not permitted. You should not assume that the information in this prospectus or in the documents incorporated by reference is accurate as of any date other than the date on the front of this prospectus or those documents.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the information incorporated herein by reference herein and therein contain statements that are not historical facts and are considered forward-looking within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act. These forward-looking statements contain projections of our future results of operations or of our financial position or state other forward-looking information. In some cases, you can identify these statements by forward-looking words such as "may," "will," "could," "should," "would," "expect," "intend," "plan," "anticipate," "believe," "estimate," "predict," "project," "potential," "continue," or the negative of such words or other similar words or phrases. We believe that it is important to communicate our future expectations to our investors. However, there may be events in the future that we are not able to accurately predict or control and that may cause our actual results to differ materially from the expectations we describe in our forward-looking statements.

Investors are cautioned not to unduly rely on forward-looking statements because they relate to future events or our future financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from any future results, levels of activity, performance or achievements expressed or implied by these forward-looking statements. Forward-looking statements include, but are not limited to, statements about:

- anticipated or estimated future results, including the risks and uncertainties associated with our future operating performance and financial position;
- market demand for and acceptance of our products;
- research, development and commercialization of new products;
- obtaining and maintaining regulatory approvals, including, but not limited to, potential regulatory delays or rejections;
- risks associated with meeting the objectives of clinical studies, including, but not limited to, delays or failures in enrollment, and the occurrence of adverse safety events;
- risks related to our ability to accomplish our business development objectives and realize the anticipated benefit of any such transactions; and
- assumptions underlying any of the foregoing.

Given these uncertainties, you should not place undue reliance on these forward-looking statements. These forward-looking statements speak only as of the date on which the statements were made and are not guarantees of future performance. Except as may be required by applicable law, we do not undertake or intend to update any forward-looking statements after the date of this prospectus or the respective dates of documents incorporated by reference herein that include forward-looking statements.

RISK FACTORS

You should carefully consider the risks described in the documents incorporated by reference in this prospectus and any prospectus supplement, as well as other information we include or incorporate by reference into this prospectus and any applicable prospectus supplement, before making an investment decision. Our business, financial condition or results of operations could be materially adversely affected by the materialization of any of these risks. The trading price of our securities could decline due to the materialization of any of these risks, and you may lose all or part of your investment. This prospectus and the documents incorporated herein by reference also contain forward-looking statements that involve risks and uncertainties. Actual results could differ materially from those

anticipated in these forward-looking statements as a result of certain factors, including the risks described in the documents incorporated herein by reference, including our most recent annual report on Form 10-K which is on file with the SEC and is incorporated herein by reference, and other documents we file with the SEC that are deemed incorporated by reference into this prospectus.

ABOUT THE COMPANY

We are a clinical-stage biopharmaceutical company focused on the development and commercialization of innovative therapeutic candidates for the treatment of cardiovascular, metabolic, and liver diseases. Our lead product candidate, MGL-3196, is a proprietary, liver-directed, selective thyroid hormone receptor-ß, or THR-ß, agonist being developed as a once-daily oral pill that can potentially be used to treat a number of disease states with high unmet medical need, including non-alcoholic steatohepatitis, or NASH. For NASH, we enrolled 125 patients in a Phase 2 clinical trial. We achieved the 12-week primary endpoint for this trial and reported the results in December 2017, and we reported topline 36-week results at the conclusion of the study in May 2018. We are also developing MGL-3196 for dyslipidemia, including genetic dyslipidemias such as heterozygous familial hypercholesterolemia, or HeFH. We enrolled 116 patients and completed a Phase 2 clinical trial in HeFH patients, and we reported the results in February 2018. In addition to the NASH and HeFH Phase 2 clinical trials, MGL-3196 has also been studied in six completed Phase 1 trials in a total of 183 subjects. MGL-3196 was safe and well-tolerated in these trials, which included a single ascending dose trial, a multiple ascending dose trial, two drug interaction trials with statins, a multiple dose mass balance study, and a single dose relative bioavailability study of tablet formulations versus capsule formulation.

We were incorporated in Delaware in September 2011. Our principal executive offices are located at 200 Barr Harbor Drive, Suite 400, West Conshohocken, Pennsylvania 19428 and our telephone number at that address is (484) 380-9263. We maintain an Internet website at the following address: www.madrigalpharma.com. The information on, or that can be accessed through, our website does not constitute part of this prospectus, and you should not rely on any such information in making the decision whether to purchase our common stock. Our common stock trades on the NASDAQ Global Market under the symbol "MDGL."

DESCRIPTION OF SECURITIES

We and/or any selling stockholder may offer shares of our common stock and preferred stock, various series of warrants to purchase common stock or preferred stock, debt securities, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt, or any combination thereof from time to time in one or more offerings under this prospectus at prices and on terms to be determined at the time of any offering. This prospectus provides you with a general description of the securities we and/or any selling stockholder may offer. Each time we and/or any selling stockholder offer a type or series of securities under this prospectus, we will provide a prospectus supplement and/or free writing prospectus that will describe the specific amounts, prices and other important terms of the securities.

Common Stock. We and/or any selling stockholder may issue and/or sell, as applicable, shares of our common stock from time to time. Holders of shares of our common stock are entitled to one vote for each share held of record on all matters to be voted on by stockholders and do not have cumulative voting rights. Subject to the preferences that may be applicable to any then outstanding preferred stock, the holders of our outstanding shares of common stock are entitled to receive dividends, if any, as may be declared from time to time by our board of directors out of legally available funds. In the event of our liquidation, dissolution or winding up, holders of our common stock will be entitled to share ratably in the net assets legally available for distribution to stockholders after the payment of all of our debts and other liabilities, subject to the satisfaction of any liquidation preference granted to the holders of any outstanding shares of preferred stock.

Preferred Stock. We may issue shares of our preferred stock from time to time, in one or more series. Our board of directors will determine the rights, preferences and privileges of the shares of each wholly unissued series, and any qualifications, limitations or restrictions thereon, including dividend rights, conversion rights, preemptive rights, terms of redemption or repurchase, liquidation preferences, sinking fund terms and the number of shares constituting any series or the designation of any series. Convertible preferred stock will be convertible into our common stock or exchangeable for other securities. Conversion may be mandatory or at the holder's option and would be at prescribed conversion rates.

If we sell any series of preferred stock under this prospectus, we will fix the rights, preferences and privileges of the preferred stock of such series, as well as any qualifications, limitations or restrictions thereon, in the certificate of designation relating to that series. We will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of any certificate of designation that describes the terms of the series of preferred stock we are offering before the issuance of that series of preferred stock. We urge you to read the applicable prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the series of preferred stock being offered, as well as the complete certificate of designation that contains the terms of the applicable series of preferred stock.

Warrants. We may issue warrants for the purchase of common stock and/or preferred stock in one or more series. We may issue warrants independently or together with common stock and/or preferred stock, and the warrants may be attached to or separate from these securities. We urge you to read the applicable prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the particular series of warrants being offered, as well as the complete warrant agreements and warrant certificates that contain the terms of the warrants. Forms of the warrant agreements and forms of warrant certificates containing the terms of the warrants being offered will be filed as exhibits to the registration statement of which this prospectus is a part or will be incorporated by reference from reports that we file with the SEC.

We will evidence each series of warrants by warrant certificates that we will issue. Warrants may be issued under an applicable warrant agreement that we enter into with a warrant agent. We will indicate the name and address of the warrant agent, if applicable, in the prospectus supplement relating to the particular series of warrants being offered.

Units. We may issue, in one or more series, units consisting of common stock, preferred stock, and/or warrants for the purchase of common stock and/or preferred stock in any combination. We urge you to read the applicable prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the series of units being offered, as well as the complete unit agreement that contains the terms of the units. We will file as exhibits to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of unit agreement and any supplemental agreements that describe the terms of the series of units we are offering before the issuance of the related series of units.

We will evidence each series of units by unit certificates that we will issue. Units may be issued under a unit agreement that we enter into with a unit agent. We will indicate the name and address of the unit agent, if applicable, in the prospectus supplement relating to the particular series of units being offered.

Debt Securities. We may issue debt securities, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt. In this prospectus, we have summarized certain general features of the debt securities. We urge you, however, to read the applicable prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the particular series of debt securities being offered, as well as the complete indenture that contains the terms of the debt securities. We will file as exhibits to the registration statement of which this prospectus is a part, the form of indenture and any supplemental agreements that describe the terms of the series of debt securities we are offering before the issuance of the related series of debt securities.

We may evidence each series of debt securities we will issue by an indenture that we enter into with a trustee. We will indicate the name and address of the trustee, if applicable, in the prospectus supplement relating to the particular series of debt securities being offered.

RATIO OF EARNINGS TO FIXED CHARGES

Our ratio of earnings to fixed charges for recently completed fiscal years and any required interim periods will be specified in a prospectus supplement or in a document that we file with the SEC and incorporate by reference in the future.

USE OF PROCEEDS

Except as described in any prospectus supplement or in any related free writing prospectus that we may authorize to be provided to you, the net proceeds received by us from our sale of the securities described in this prospectus will be added to our general funds and will be used for our general corporate purposes. From time to time, we may engage in additional public or private financings of a character and amount which we may deem appropriate. Unless otherwise set forth in a prospectus supplement, we will not receive any proceeds from the sale of securities by any selling stockholder.

SELLING STOCKHOLDERS

Selling stockholders are persons or entities that, directly or indirectly, have acquired or will from time to time acquire from us, our securities. Such selling stockholders may be parties to registration rights agreements with us, or we otherwise may have agreed or will agree to register their securities for resale. The initial purchasers of our securities, as well as their transferees, pledges, donees or

successors, all of whom we refer to as "selling stockholders," may from time to time offer and sell our securities pursuant to this prospectus and any applicable prospectus supplement.

The applicable prospectus supplement will set forth the name of each of the selling stockholders and the number of securities beneficially owned by such selling stockholder that are covered by such prospectus supplement. The applicable prospectus supplement will also disclose whether any of the selling stockholders has held any position or office with, has been employed by or otherwise has had a material relationship with us during the three years prior to the date of the applicable prospectus supplement.

PLAN OF DISTRIBUTION

We and/or any selling stockholder may sell our securities from time to time in one or more transactions. We and/or any selling stockholder may sell our securities to or through agents, underwriters, dealers, remarketing firms or other third parties or directly to one or more purchasers or through a combination of any of these methods. In some cases, we and/or any selling stockholder or dealers acting with us and/or any selling stockholder or on behalf of us and/or any selling stockholder may also purchase our securities and reoffer them to the public. We and/or any selling stockholder may also offer and sell, or agree to deliver, our securities pursuant to, or in connection with, any option agreement or other contractual arrangement.

Agents whom we designate may solicit offers to purchase our securities.

- We and/or any selling stockholder will name any agent involved in offering or selling our securities, and disclose any commissions that we will pay to the agent, in the applicable prospectus supplement.
- Unless we and/or any selling stockholder indicate otherwise in the applicable prospectus supplement, agents will act on a best efforts basis for the period of their appointment.
- Agents may be deemed to be underwriters under the Securities Act, of any of our securities that they offer or sell.

We and/or any selling stockholder may use an underwriter or underwriters in the offer or sale of our securities.

- If we and/or any selling stockholder use an underwriter or underwriters, we will execute an underwriting agreement with the underwriter or underwriters at the time that we reach an agreement for the sale of our securities.
- We and/or any selling stockholder will include the names of the specific managing underwriter or underwriters, as well as the names of any other underwriters, and the terms of the transactions, including the compensation the underwriters and dealers will receive, in the applicable prospectus supplement.
- The underwriters will use the applicable prospectus supplement, together with the prospectus, to sell our securities.

We may use a dealer to sell our securities.

- If we and/or any selling stockholder use a dealer, we will sell our securities to the dealer, as principal.
- The dealer will then sell our securities to the public at varying prices that the dealer will determine at the time it sells our securities.
- We and/or any selling stockholder will include the name of the dealer and the terms of the transactions with the dealer in the applicable prospectus supplement.

We and/or any selling stockholder may solicit directly offers to purchase our securities, and we may directly sell our securities to institutional or other investors. We and/or any selling stockholder will describe the terms of direct sales in the applicable prospectus supplement.

We and/or any selling stockholder may engage in at the market offerings into an existing trading market in accordance with Rule 415(a)(4) of the Securities Act.

We and/or any selling stockholder will indemnify agents, underwriters and dealers against certain liabilities, including liabilities under the Securities Act. Agents, underwriters and dealers, or their

affiliates, may be customers of, engage in transactions with or perform services for us or our respective affiliates, in the ordinary course of business.

We and/or any selling stockholder may authorize agents and underwriters to solicit offers by certain institutions to purchase our securities at the public offering price under delayed delivery contracts.

- If we and/or any selling stockholder use delayed delivery contracts, we will disclose that we are using them in the prospectus supplement and will tell you when we will demand payment and when delivery of our securities will be made under the delayed delivery contracts.
- These delayed delivery contracts will be subject only to the conditions that we describe in the prospectus supplement.
- We and/or any selling stockholder will describe in the applicable prospectus supplement the commission that underwriters and agents soliciting purchases of our securities under delayed delivery contracts will be entitled to receive.

Unless otherwise specified in connection with a particular underwritten offering of our securities, the underwriters will not be obligated to purchase offered securities unless specified conditions are satisfied, and if the underwriters do purchase any offered securities, they will purchase all offered securities.

In connection with underwritten offerings of the offered securities and in accordance with applicable law and industry practice, the underwriters in certain circumstances are permitted to engage in certain transactions that stabilize the price of our securities. Such transactions consist of bids or purchases for the purpose of pegging, fixing or maintaining the price of our securities. If the underwriters create a short position in our securities in connection with the offering (*i.e.*, if they sell more securities than are set forth on the cover page of the applicable prospectus supplement), the underwriters may reduce that short position by purchasing our securities in the open market or as otherwise provided in the applicable prospectus supplement. The underwriters may also impose a penalty bid, whereby selling concessions allowed to dealers participating in the offering may be reclaimed if the securities sold by them are repurchased in connection with stabilization transactions. In general, purchases of a security for the purpose of stabilization or to reduce a short position could cause the price of the security to be higher than it might be in the absence of such purchases. The imposition of a penalty bid might also have an effect on the price of our securities to the extent that it were to discourage resales of our securities. The underwriters are not required to engage in these activities and may end any of these activities at any time.

We and/or any selling stockholder may effect sales of securities in connection with forward sale, option or other types of agreements with third parties. Any distribution of securities pursuant to any forward sale agreement may be effected from time to time in one or more transactions that may take place through a stock exchange, including block trades or ordinary broker's transactions, or through broker-dealers acting either as principal or agent, or through privately-negotiated transactions, or through an underwritten public offering, or through a combination of any such methods of ale, at market prices prevailing at the time of sale, prices relating to such prevailing market prices or at negotiated or fixed prices.

The specific terms of the lock-up provisions, if any, in respect of any given offering will be described in the applicable prospectus supplement.

In compliance with the guidelines of the Financial Industry Regulatory Authority, or FINRA, the maximum consideration or discount to be received by any FINRA member or independent broker dealer may not exceed 8.0% of the aggregate amount of the securities offered by this prospectus.

LEGAL MATTERS

The validity of the securities being offered by this prospectus will be passed upon by Baker & Hostetler, LLP, Costa Mesa, California.

EXPERTS

The financial statements and management's assessment of the effectiveness of internal control over financial reporting (which is included in Management's Report on Internal Control over Financial Reporting) incorporated in this prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2017 have been so incorporated in reliance on the report of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

$200,000,000

363,625 Shares Offered by the Selling Stockholders

Common Stock

PROSPECTUS SUPPLEMENT

, 2018

Goldman Sachs & Co. LLC

We have not authorized anyone to provide any information other than that contained or incorporated by reference in this prospectus supplement and accompanying prospectus or any free writing prospectus that we or the underwriter provide you in connection with the offering. We take no responsibility for, and cannot provide any assurance as to the reliability of, any other information that others may give you. We are not making an offer of these securities in any state where the offer is not permitted. You should not assume that the information contained in or incorporated by reference in this prospectus supplement and accompanying prospectus is accurate as of any date other than the date on the front of this prospectus supplement.

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