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

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2022

OR

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

For the transition period from_____ to _____

Commission file number: 001-33277

MADRIGAL PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**04-3508648**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
Four Tower Bridge **200 Barr Harbor Drive, Suite 200** **West Conshohocken, Pennsylvania**	**19428**
(Address of Principal Executive Offices)	**(Zip Code)**

Registrant's telephone number, including area code: (267) 824-2827
Former name, former address and former fiscal year, if changed since last report:
Securities registered pursuant to Section 12(b) of the Exchange Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 Par Value Per Share	**MDGL**	**The NASDAQ Stock Market LLC**

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

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

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

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

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

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

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

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☒

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b). ☐

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

The aggregate market value of the voting stock held by non-affiliates of the registrant based upon the closing sale price of the registrant's common stock on June 30, 2022 (the last business day of the registrant's most recently completed second fiscal quarter), as reported on the Nasdaq Global Market, was $984,861,131. For purposes of this calculation, directors and executive officers of the registrant have been deemed affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

As of February 20, 2023, the registrant had 18,138,012 shares of common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Certain information required by Part III, Items 10-14 of this Form 10-K is incorporated by reference to the registrant's definitive Proxy Statement for the 2023 Annual Meeting of Stockholders to be filed with the Securities and Exchange Commission pursuant to Regulation 14A not later than 120 days after the end of the fiscal year covered by this Form 10-K, provided that if such Proxy Statement is not filed within such period, such information will be included in an amendment to this Form 10-K to be filed within such 120-day period.

Auditor Firm Id: 238 Auditor Name: PricewaterhouseCoopers LLP Auditor Location: Philadelphia, Pennsylvania

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K for the fiscal year ended December 31, 2022 includes "forward-looking statements" made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, that are based on our beliefs and assumptions and on information currently available to us, but are subject to factors beyond our control Forward-looking statements: reflect management's current knowledge, assumptions, judgment and expectations regarding future performance or events; include all statements that are not historical facts; and can be identified by terms such as "accelerate," "achieve," "allow," "anticipates," "appear," "be," "believes," "can," "continue," "could," "demonstrates," "design," "estimates," "expectation," "expects," "forecasts," "future," "goal," "help," "hopeful," "inform," "informed," "intends," "may," "might," "on track," "planned," "planning," "plans," "positions," "potential," "powers," "predicts," "predictive," "projects," "seeks," "should," "will," "will achieve," "will be," "would" or similar expressions and the negatives of those terms. In particular, forward-looking statements contained in or incorporated by reference to this Annual Report relate to, among other things,

- Anticipated or estimated future results, including the risks and uncertainties associated with our future operating performance and financial position,
- Our possible or assumed future results of operations and expenses, business strategies and plans (including ex-U.S. launch/partnering plans), capital needs and financing plans, including incurrence of indebtedness and compliance with debt covenants under the Loan and Security Agreement with Hercules Capital, Inc., as agent and lender, market trends, market sizing, competitive position, industry environment and potential growth opportunities, among other things,
- Our ability to delay certain research activities and related clinical expenses as necessary,
- Our projected resources and sufficiency of capital to fund our operating expenses through the projected commercial launch of resmetirom, assuming Food and Drug Administration ("FDA") approval is obtained;
- Our clinical trials, including the anticipated timing of disclosure, presentations of data from, or outcomes from our trials,
- Research and development activities, and the timing and results associated with the future development of our lead product candidate, resmetirom (formerly known as MGL-3196), including projected market size, sector leadership, and patient treatment estimates for non-alcoholic steatohepatitis ("NASH") and nonalcoholic fatty liver disease ("NAFLD") patients,
- The timing and completion of projected future clinical milestone events, including enrollment, additional studies, top-line data and open label projections,
- Resmetirom's potential to be a cost-effective specialty therapy for NASH patients with significant liver fibrosis,
- Plans, objectives and timing for making a Subpart H (Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses) submission to the FDA,
- Projections or objectives for obtaining accelerated or full approval for resmetirom for NASH patients with significant fibrosis (or non-cirrhotic NASH patients) and NASH patients with compensated cirrhosis,
- Our primary and key secondary study endpoints for resmetirom, and the potential for achieving such endpoints and projections, including NASH resolution, safety, fibrosis treatment, cardiovascular effects and lipid treatment with resmetirom,

- Optimal dosing levels for resmetirom and projections regarding potential NASH or NAFLD and potential patient benefits with resmetirom, including future NASH resolution, safety, fibrosis treatment, cardiovascular effects, lipid treatment and/or biomarker effects with resmetirom,
- Our ability to address the unmet needs of patients suffering from NASH with significant fibrosis,
- The potential efficacy and safety of resmetirom for non-cirrhotic NASH patients and cirrhotic NASH patients,
- The potential for resmetirom to become the best-in-class and/or first-to-market treatment option for patients with NASH and liver fibrosis;
- Anticipated or estimated future results of operations and expenses as we expand our resmetirom clinical development program and our commercial development program;
- Ex-U.S. launch/partnering plans,
- The ability to develop clinical evidence demonstrating the utility of non-invasive tools and techniques to screen and diagnose NASH and/or NAFLD patients,
- The predictive power of liver fat reduction with resmetirom, as measured by non-invasive tests, on NASH resolution and/or fibrosis reduction or improvement, and potential NASH or NAFLD patient risk profile benefits with resmetirom,
- The predictive power of liver fat, liver volume changes or MAST scores for NASH and/or NAFLD patients,
- The predictive power of NASH resolution and/or liver fibrosis reduction with resmetirom or improvement using non-invasive tests, including the use of ELF, FibroScan, MRE and/or MRI-PDFF,
- The predictive power of non-invasive tests generally, including for purposes of diagnosing NASH, monitoring patient response to resmetirom, or recruiting and conducting a NASH clinical trial,
- Market demand for and acceptance of our products,
- Research, development and commercialization of new products,
- The potential for resmetirom to be an effective treatment for other disease indications,
- Obtaining and maintaining regulatory approvals, including, but not limited to, potential regulatory delays or rejections,
- Risks associated with meeting the objectives of our clinical studies, including, but not limited to our ability to achieve enrollment objectives concerning patient numbers (including an adequate safety database), outcomes objectives and/or timing objectives for our studies, any delays or failures in enrollment, the occurrence of adverse safety events, and the risks of successfully conducting trials that are substantially larger, and have patients with different disease states, than our past trials,
- our continued reliance on third-party contract manufacturers for the manufacture of our product candidates, including resmetirom,
- Risks related to the effects of resmetirom's mechanism of action and our ability to accomplish our business and business development objectives and realize the anticipated benefit of any such transactions, and
- Assumptions underlying any of the foregoing.

We caution you that the foregoing list may not include all of the forward-looking statements made in this Annual Report. Although management presently believes that the expectations reflected in such forward-looking

statements are reasonable, it can give no assurance that such expectations will prove to be correct and you should be aware that actual results could differ materially from those contained in the forward-looking statements.

Forward-looking statements are subject to a number of risks and uncertainties including, but not limited to: our clinical and commercial development of resmetirom; enrollment and trial outlook uncertainties, generally, based on blinded, locked or limited trial data and in relation to COVID-19-related measures and individual precautionary measures that may be implemented or continued for an uncertain period of time; our potential inability to raise sufficient capital to fund our ongoing operations as currently planned or to obtain financings on terms similar to those we have arranged in the past; our ability to service our indebtedness and otherwise comply with our debt covenants; outcomes or trends from competitive studies; future topline data timing or results; the risks of achieving potential benefits in studies that includes substantially more patients, and patients with different disease states, than our prior studies; limitations associated with early stage or non-placebo controlled study data; the timing and outcomes of clinical studies of resmetirom; and the uncertainties inherent in clinical testing. Undue reliance should not be placed on forward-looking statements, which speak only as of the date they are made. Madrigal undertakes no obligation to update any forward-looking statements to reflect new information, events or circumstances after the date they are made, or to reflect the occurrence of unanticipated events. Please refer to Madrigal's submissions filed or furnished with the U.S. Securities and Exchange Commission for more detailed information regarding these risks and uncertainties and other factors that may cause actual results to differ materially from those expressed or implied. We specifically discuss these risks and uncertainties in greater detail in the section entitled "Risk Factors" in Part I, Item 1A of this Annual Report, as well as in our other filings with the SEC. You should read this Annual Report, and the other documents that we file or have filed with the SEC, with the understanding that our actual future results may be materially different from the results expressed or implied by these forward-looking statements.

Moreover, we operate in an evolving environment. New risks and uncertainties emerge from time to time and it is not possible for our management to predict all risks and uncertainties, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual future results to be materially different from those expressed or implied by any forward-looking statements.

Except as required by applicable law or the rules of the NASDAQ Stock Market, or NASDAQ, we assume no obligation to update any forward-looking statements publicly, or to update the reasons actual results could differ materially from those anticipated in these forward-looking statements, even if new information becomes available in the future. We qualify all of our forward-looking statements by these cautionary statements.

RISK FACTOR SUMMARY

The following is a summary of the principal risk factors that make an investment in our common stock speculative or risky. Before you invest in our securities, you should read the following summary together with the more detailed description of material risks described in the section entitled "Risk Factors" in Part I, Item 1A of this Annual Report and the other information contained in this Annual Report.

Risks Relating 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.
- Our business depends on the success of resmetirom, which is still in clinical development and has not completed a pivotal outcomes trial. If we are unable to obtain regulatory approval for and successfully commercialize resmetirom, or we experience significant delays in doing so, our business will be materially harmed.
- Clinical trials are very expensive, time-consuming and difficult to design and implement and involve uncertain outcomes. 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 may not have favorable results in later clinical trials or receive regulatory approval.
- Because resmetirom 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 and our ability to realize a benefit, if any, from Fast Track designation or any Subpart H application may be limited or unavailable.
- 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.
- 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.
- We depend on enrollment of patients in our clinical trials for our product candidates. If we encounter difficulties enrolling patients in our clinical trials, including those arising out of COVID-19**,** our clinical development activities could be delayed or otherwise adversely affected.
- 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.
- 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.
- We operate in a highly competitive and rapidly changing industry, and our product candidates may become obsolete.
- 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.

- 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.
- The continuation or worsening of the COVID-19 pandemic could affect our ability to complete our ongoing clinical trials, disrupt regulatory activities and delay or disrupt commercialization of resmetirom, and may have other adverse effects on our stock price and business operations.
- 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.
- The uncertainty associated with pharmaceutical reimbursement and related matters may adversely affect our business.
- If we fail to develop and commercialize other product candidates, we may be unable to grow our business.
- Our internal computer systems, or those of our third-party collaborators, service providers, contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our development programs and have a material adverse effect on our reputation, business, financial condition or results of operations.

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 resmetirom granted to us by Hoffmann-La Roche.
- 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.
- Our success depends on our ability to protect our intellectual property and our proprietary technologies.
- 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.
- 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.
- We may not be successful in obtaining or maintaining necessary rights to our product candidates through acquisitions and in-licenses.
- We may not be able to protect our intellectual property rights throughout the world.

Risks Relating to Our Financial Position and Need for Capital

- If we fail to obtain the capital necessary to fund all of our planned operations, we may be unable to successfully develop and commercialize resmetirom and other future product candidates.
- 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.

Risks Relating to our Indebtedness

- Our Loan and Security Agreement contains restrictive and financial covenants that may limit our operating flexibility.
- Our failure to comply with the covenants or other terms of the Loan Agreement, including as a result of events beyond our control, could result in a default under the Loan Agreement that could materially and adversely affect our business

Risks Relating to Ownership of Our Common Stock

- The price of our common stock has been, and may continue to be, volatile.
- A small number of our stockholders own a substantial amount of our outstanding common stock and may be deemed to have substantial control over us; therefore, your ability to influence corporate matters may be limited.
- 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.
- 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.
- 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.

PART I

Item 1. Business

References in this Annual Report on Form 10-K to Madrigal, the Company, we, our and us refer to Madrigal Pharmaceuticals, Inc. "Madrigal" is a registered trademark of Madrigal Pharmaceuticals, Inc. in the U.S. and/or other countries. Other trademarks or service marks appearing in this report may be trademarks or service marks of other owners.

Executive Overview

Our Focus. We are a clinical-stage biopharmaceutical company pursuing novel therapeutics for nonalcoholic steatohepatitis, or NASH. Our lead product candidate, resmetirom, is a proprietary, liver-directed, selective thyroid hormone receptor-ß, or THR-ß, agonist being developed as a once-daily oral pill for the treatment of NASH.

Our Patient Market Opportunity. 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. NASH can progress to cirrhosis or liver failure, require liver transplantation and can also result in liver cancer. Progression of NASH to end stage liver disease will soon surpass all other causes of liver failure requiring liver transplantation. Importantly, beyond these critical conditions, NASH and NAFLD patients additionally suffer heightened cardiovascular risk and, in fact, die more frequently from cardiovascular events than from liver disease. NASH and NAFLD have grown as a consequence of rising worldwide obesity-related disorders. In the United States, NAFLD is estimated to affect approximately 25% of the population, and approximately 25% of those will progress from NAFLD to NASH. Current estimates place NASH prevalence at approximately 22 million people in the United States by 2024, 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.

Our Completed Studies. For NASH, we enrolled 125 patients in a Phase 2 clinical trial with resmetirom. 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 also completed a 36-week, open-label extension study in 31 participating NASH patients from our Phase 2 clinical trial, which included 14 patients who received placebo in the main study.

On December 18, 2019 the Company announced it had opened for enrollment MAESTRO-NAFLD-1, a 52-week, non-invasive, multi-center, double-blind, placebo-controlled Phase 3 clinical study of patients with biopsy-confirmed or presumed NASH recruited from sites in the U.S. Key endpoints are safety, including safety biomarkers. Secondary endpoints include LDL cholesterol, lipid biomarkers, MRI-PDFF, NASH and fibrosis biomarkers. Except for serial liver biopsies, the study protocol is similar to the MAESTRO-NASH study (discussed below under "—Our Ongoing and Planned Studies"), with resmetirom doses of 80 mg or 100 mg or placebo. Enrollment objectives for this study were exceeded, with approximately 1,300 patients enrolled overall. The MAESTRO-NAFLD-1 study will help support the adequacy of the safety database at the time of NDA submission for Subpart H approval for treatment of patients with NASH with fibrosis. In November of 2021, we reported data from the open label non-cirrhotic arm of MAESTRO-NAFLD-1, and in January 2022 we announced that we achieved primary and secondary endpoints for the double-blind portion of MAESTRO-NAFLD-1, as summarized in "- Key Developments" below.

Our Ongoing and Planned Studies. On March 28, 2019, the Company announced that it had initiated MAESTRO-NASH, a Phase 3 trial in NASH with its once daily, oral thyroid hormone receptor beta selective agonist, resmetirom. This double-blind, placebo-controlled study is being conducted at more than 220 sites in the United States and the rest of the world. MAESTRO-NASH is a multicenter, randomized, double-blind, placebo-

controlled Phase 3 study of resmetirom in patients with liver biopsy-confirmed NASH and was initiated in March 2019. The subpart H portion of the study enrolled more than 1,000 patients with biopsy-proven NASH (at least half with F3 (advanced) fibrosis, the remainder F2 or F1B (moderate fibrosis) with a few earlier F1 patients), randomized 1:1:1 to receive once-daily resmetirom 80 mg, resmetirom 100 mg, or placebo. After 52 weeks of treatment, a second liver biopsy is performed. The dual primary surrogate endpoints on biopsy are NASH resolution with ≥2-point reduction in NAS (NAFLD Activity Score), and with no worsening of fibrosis OR a 1-point decrease in fibrosis with no worsening of NAS. Achievement of either primary endpoint is considered a successful trial outcome. A key secondary endpoint is lowering of LDL-C. All patients enrolled in the MAESTRO-NASH study (up to 2,000 in total) continue on therapy after the initial 52-week treatment period for up to 54 months to accrue and measure hepatic clinical outcome events including progression to cirrhosis on biopsy (52 weeks and 54 months) and hepatic decompensation events, as well as all-cause mortality. In December 2022, we reported topline results from the subpart H portion of the study: resmetirom achieved both primary endpoints with both daily oral doses, 80 mg and 100 mg, relative to placebo, as summarized in "- Key Developments" below.

On July 13, 2021 we announced first patient dosed in a planned 52-week open label active treatment extension study of MAESTRO-NAFLD-1, named MAESTRO-NAFLD-Open Label Extension (OLE). The OLE study allows patients who complete MAESTRO-NAFLD-1 to consent to 52 weeks of active treatment with resmetirom, making this treatment available to both patients who were assigned to placebo in MAESTRO-NAFLD-1 and patients who were on resmetirom in MAESTRO-NAFLD-1.

In August 2022, Madrigal initiated MAESTRO-NASH-OUTCOMES, a randomized double-blind placebo-controlled study in approximately 700 patients with early NASH cirrhosis to allow for noninvasive monitoring of progression to liver decompensation events. A positive outcome is expected to support the full approval of resmetirom for noncirrhotic NASH, potentially accelerating the timeline to full approval. In addition, this study has the potential to support an additional indication for resmetirom in patients with well-compensated NASH cirrhosis.

The following chart summarizes the status of our product candidate development programs for resmetirom:

Clinical Trial	Status	Primary Outcome
Phase 2 **MGL-3196-05** NCT02912260	Completed	Relative change in hepatic fat (by MRI-PDFF) at Week 12
Phase 3 **MAESTRO-NASH** NCT03900429	Subpart H (52 weeks) – Recruited	NASH resolution or fibrosis improvement on serial liver biopsy at Week 52
	Outcomes (54 months) – Ongoing	Study continues to outcomes. Composite endpoint includes histologic conversion to cirrhosis, hepatic decompensation events, MELD ≥15, liver transplant, & all-cause mortality
Phase 3 **MAESTRO-NAFLD-1** (presumed NASH) NCT04197479	Completed (OL Arms Ongoing)	Safety & tolerability as measured by incidence of AEs over 52 weeks in >1200 patients
	Ongoing	Phase 3 **MAESTRO-NAFLD-OLE** (NCT04951219) 52-week extension to MAESTRO-NAFLD-1 in >700 patients: Safety & tolerability by incidence of AEs over 52 weeks
Phase 3 **MAESTRO-NASH-OUTCOMES** NCT05500222	Initiated	Event-driven clinical outcome to decompensated cirrhosis in patients with well-compensated NASH cirrhosis

Key Developments

MAESTRO-NASH TRIAL. In December 2022, Madrigal announced topline results from the pivotal Phase 3 MAESTRO-NASH biopsy study of resmetirom. Madrigal reported that resmetirom achieved both primary endpoints with both daily oral doses, 80 mg and 100 mg, relative to placebo.

Patients meeting eligibility requirements for MAESTRO-NASH were randomized 1:1:1 to receive resmetirom 80 mg, resmetirom 100 mg, or placebo taken orally once daily. Baseline characteristics in the 966 randomized patients in the primary analysis NASH population (ITT, safety population) were balanced across treatment arms and include age 57 (10) (mean (SD)), female 56%, white 89%, Hispanic 21%, BMI 36 (7) kg/m2, type 2 diabetes 67%, hypertension 78%, dyslipidemia 71%, hypothyroidism 13%, FibroScan, kilopascals (kPa) 13 (7), CAP 348 (38), MRI-PDFF 18% (7), FIB-4 1.4 (0.7), ALT 55 (32) IU, AST 41 (23) IU, LDL 99 (40) mg/dL, triglycerides 188 (132) mg/dL, hemoglobin A1C 6.6 (1) %, ELF 9.8 (0.9). Medications included 49% on statins, 14% on GLP-1 agonists, 14% on SGLT2 inhibitors. Baseline liver biopsy fibrosis scores included F3 (~60%), F2 (~35%), F1B (~5%) (primary analysis population) with 84% with NAS ≥5 based on independent primary glass slide reads of the entire study by two central pathologists.

A second biopsy was conducted after 52 weeks of treatment for assessment of the dual primary endpoints. The primary efficacy analysis assessed histological response at 52 weeks in 955 patients with biopsy-confirmed NASH with fibrosis (modified intent-to-treat (mITT) population) that excluded 11 ITT patients who had their Week 52 biopsy after Week 60 due to COVID-related reasons per regulatory guidelines. Patients without a second biopsy due to early study discontinuation or missing liver biopsy (~17% across treatment arms) were included and considered as non-responders in the primary efficacy analyses (mITT). The compliance to treatment was high and minimally impacted by COVID-19 pandemic restrictions.

Dual Primary Endpoints (52 Weeks) and Key Secondary Endpoint (24 weeks)

Primary Endpoint	Resmetirom 80 mg (n=316)	p-value	Resmetirom 100 mg (n=321)	p-value	Placebo (n=318)
NASH resolution (ballooning o, inflammation 0,1) with ≥2-point reduction in NAS and no worsening of fibrosis	26%	<0.0001	30%	<0.0001	10%
≥-stage improvement in fibrosis with no worsening of NAS	24%	0.0002	26%	<0.0001	14%
Key Secondary Endpoint					
LDL-C lowering (24 weeks)	-12%	<0.0001	-16%	<0.0001	1%

All biopsies were read independently by two central pathologists. Each pathologist's scores showed a similar statistically significant magnitude of response at both doses for both liver biopsy endpoints. Biopsy endpoints were achieved independent of baseline fibrosis stage or diabetes status, including similar statistical significance and magnitude of effect at both doses in subgroups of F2, F3, and F2/F3 patients. Other secondary liver biopsy endpoints that were achieved at both doses include ≥2 point reduction in NAS with no worsening of fibrosis, ≥2 point reduction in NAS with ≥1-stage improvement in fibrosis, NASH resolution (with ≥2 point reduction in NAS) with ≥1-stage improvement in fibrosis, and a 2-stage reduction in fibrosis without worsening of NAS.

Multiple secondary endpoints were achieved, including statistically significant reduction from baseline in liver enzymes (ALT, AST and GGT). Reductions in atherogenic lipids and lipoproteins, fibrosis biomarkers and imaging tests (MRI-PDFF, CAP and liver stiffness measures) were observed in resmetirom treatment arms as compared with placebo. MAESTRO-NASH included many biomarker and imaging assessments that may be used in real world clinical practice to identify appropriate patients for treatment and monitor response to resmetirom, if approved.

Resmetirom was safe and well-tolerated at both the 80 mg and 100 mg doses. The frequency of serious adverse events (SAEs) was similar across treatment arms: 11.8%, 12.7% and 12.1% for the 80 mg, 100 mg, and placebo groups, respectively. The rate of study discontinuation for adverse events was low: 2.8%, 7.7% and 3.7% for the 80 mg, 100 mg and placebo groups, respectively. SAEs occurred at expected rates based on the patient population.

Consistent with previous Phase 2 and Phase 3 data, the most common adverse events reported with greater frequency in the resmetirom groups versus placebo were an excess of generally mild and transient diarrhea at the beginning of therapy, in 28%, 34%, 16% in the 80 mg, 100 mg and placebo groups, respectively, and generally mild nausea that occurred at rates of 22%, 19% and 13% in the 80 mg, 100 mg and placebo arms, respectively.

MAESTRO-NASH is an ongoing blinded Phase 3 clinical trial, and enrolled patients continue on therapy after the Week 52 liver biopsy for up to a total of 54 months to accrue hepatic clinical outcome events including histologic conversion to cirrhosis and hepatic decompensation events.

MAESTRO-NAFLD-1. In January 2022, Madrigal announced topline results from the Phase 3 MAESTRO-NAFLD-1 safety study of resmetirom. Madrigal reported that resmetirom demonstrated statistical significance for primary and key secondary endpoints summarized below, from the double-blind placebo-controlled 969-patient portion of the study. These endpoints indicated that resmetirom (1) was well-tolerated at 80 and 100 mg in patients treated for 52 weeks, (2) provided significant and clinically relevant reductions in liver fat as measured by MRI-PDFF and (3) significantly reduced atherogenic lipids, including LDLc, apolipoprotein B and triglycerides.

A total of 972 patients were randomized in the double-blind arms of the MAESTRO-NAFLD-1 study: 969 patients were included in the safety population and 943 patients in a modified intent-to-treat population for evaluation of key secondary and other endpoints. Important inclusion criteria included the presence of three risk factors of metabolic syndrome, a level of liver fibrosis (measured by FibroScan) consistent with a range of stages of liver fibrosis, and >=8% liver fat (measured by MRI-PDFF).

Adverse events observed in the MAESTRO-NAFLD-1 trial were generally mild to moderate in severity. The frequency of serious adverse events was similar across treatment arms and discontinuation for adverse events was low.

Consistent with published data, the most common adverse event reported with greater frequency in the resmetirom groups vs placebo was generally mild diarrhea or increased stool frequency at the beginning of therapy, which occurred in 9% and ~17% over the placebo rate in the 80 and 100 mg dose groups, respectively.

	Resmetirom 80 mg	**Resmetirom 100 mg**	**Placebo**
Safety population	(N=327)	(N=324)	(N=318)
At least one TEAE	289 (88.4)	279 (86.1)	260 (81.8)
At least one Serious TEAE	20 (6.1)	24 (7.4)	20 (6.3)
TEAE ≥ Grade 3 Severity	26 (8.0)	29 (9.0)	29 (9.1)
AE discontinuations from study	All treatments combined, n=21; (2.17%)		

	Resmetirom 80 mg	Resmetirom 100 mg	Placebo
Maximum NCI CTCAE Severity Grade			
Grade 1	99 (30.3)	99 (30.6)	92 (28.9)
Grade 2	164 (50.2)	151 (46.6)	139 (43.7)
AEs over 10%			
Diarrhea	76 (23.2)	101 (31.2)	44 (13.8)
Nausea	38 (11.6)	59 (18.2)	25 (7.9)

AE (adverse event); TEAE (treatment emergent adverse event); NCI (National Cancer Institute); CTCAE (Common Terminology Criteria for Adverse Events)

The following hierarchically-controlled key secondary endpoints were reported for both the 80 and 100 mg resmetirom dose groups. Resmetirom provided significant reductions in liver fat as measured by MRI-PDFF and reduced atherogenic lipids, including LDLc, apolipoprotein B and triglycerides. Open-label arm data is reported in the far left column below and double-blind arm data are reported in the remaining columns below. Although both arms were randomized in MAESTRO-NAFLD-1, lipid reductions were numerically greater in the 100 mg open label treatment arm compared to the 100 mg double-blind arm, and we believe this is due to greater visit and dose interruptions experienced by open-label arm patients during the height of the COVID-19 pandemic, as patients in the open-label active 100 mg treatment arm were less impacted by COVID-related dose interruptions than double-blind patients.

	Resmetirom 100 mg OL	Resmetirom 80 mg	p-value	Resmetirom 100 mg	p-value	Placebo
LDLc %CFB (SE) (Week 24)	-21 (1.9)	-12.7 (2.1)	<.0001	-14.4 (2.1)	<.0001	-1.7 (2.0)
ApoB %CFB (SE) (Week 24)	-22 (1.5)	-14.6 (1.5)	<.0001	-16.6 (1.6)	<.0001	-0.1 (1.5)
MRI-PDFF %CFB (Week 16)	-49%	-41%	<.0001	-48%	<.0001	-6%
Liver volume PDFF correction %CFB	-60%					
MRI-PDFF %CFB (Week 52)	-53%	-43%	<.0001	-48%	<.0001	-8%
Liver volume PDFF correction %CFB	-61%					
Triglycerides baseline >150 mg/dL, CFB (SE)	-65 (8.3)	-55.6 (8.6)	NA	-59 (6.5)	NA	-6.9 (16.1)
Triglycerides baseline >150 mg/dL (geomean) %CFB (95% CI)	-25 (3.1)	-19.5 (-27.0 to -11.1)	=.0005	-21.5 (-28.0 to -14.3)	<.0001	-2.1 (-10.6 to 7.4)

CFB (change from baseline); SE (standard error); APOB (Apolipoprotein B); MRI-PDFF (magnetic resonance imaging proton density fat-fraction); CI (confidence interval); OL, open label non-cirrhotic arm randomized concurrently with double-blind arms

MASESTRO-NASH OUTCOMES. In August 2022, we announced initiation of MAESTRO-NASH OUTCOMES, a Phase 3, double-blind, randomized, placebo-controlled study that will noninvasively measure progression to liver decompensation events in approximately 700 patients with compensated NASH cirrhosis.

The primary endpoint of MAESTRO-NASH OUTCOMES is the incidence of composite liver-related outcome events, including all-cause mortality, liver transplant, hepatic decompensation (ascites, hepatic encephalopathy, gastroesophageal variceal hemorrhage), and confirmed increase of Model for End-Stage Liver Disease (MELD) score from <12 to ≥15 due to progression of NASH cirrhosis. Key inclusion criteria are well-compensated NASH cirrhosis (Child-Pugh A) and presence of three metabolic risk factors (metabolic syndrome). Patients will be randomized 3:1 in a blinded manner to receive 80 mg resmetirom or matching placebo, given orally once daily. The study duration is expected to be two to three years for accrual of the required number of composite clinical outcome events.

A positive outcome is expected to support the full approval of resmetirom for noncirrhotic NASH, potentially accelerating the timeline to full approval. In addition, this study has the potential to support an additional indication for resmetirom in patients with well-compensated NASH cirrhosis.

RESMETIROM PHASE 2 CLINICAL TRIAL in NASH. As summarized above, the Company successfully completed its Phase 2 clinical trial in NASH in 2018. In this clinical trial, resmetirom demonstrated statistical significance in the primary endpoint ($p<0.0001$), the relative reduction of liver fat compared with baseline on magnetic resonance imaging-estimated proton density fat fraction, or MRI-PDFF, at 12-weeks which was reported in December 2017, and 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, which was reported in May 2018. This clinical trial was published in the Lancet in November, 2019.

Lead Product Candidate—Resmetirom

We believe that resmetirom may be the first THR-agonist product candidate in development for NASH that selectively targets the THR-ß pathway. Active thyroid hormone, known as T3, interacts with two nuclear receptors, THR-α, which is the predominant receptor expressed in most human tissues, including heart and bone, and THR-ß, which has more restricted tissue expression, and is the predominant receptor responsible for metabolic actions in the liver, including both cholesterol- and TG-lowering. Selective activation of the THR-ßreceptor in liver tissue is believed to favorably affect cholesterol and lipoprotein levels via multiple mechanisms, which may be complementary to those of other lipid-lowering therapies such as statin drugs. We believe that these characteristics of THR-ß activation by resmetirom will in turn lead to clinically meaningful reductions in LDL-C, and plasma and liver TGs.

We believe that resmetirom is the first selective small molecule THR-ß agonist compound. Resmetirom, along with MGL-3745, a potential backup compound to resmetirom, was discovered at Hoffmann-La Roche, or Roche, in Nutley, New Jersey, by utilizing a novel functional assay that, unlike a simple receptor binding assay, assessed the functional activity of compounds which interacted with thyroid hormone receptors. In a published study by Madrigal and Roche in the Journal of Medicinal Chemistry using this functional assay, resmetirom was shown to be highly selective for the THR-ß receptor, with almost no effect on THR-α, unlike other compounds purported in published studies to be ß -selective based on binding affinity, but which were shown to equally activate THR-α and THR-ß in the novel functional assay.

We believe that the ß-selectivity and liver-targeting properties of resmetirom are critically important for resmetirom's beneficial metabolic actions in the liver, and enable avoidance of safety issues associated with THR-α activation by thyroid hormone and/or less selective THR agonists in tissues such as heart and bone. In a variety of preclinical animal model studies, resmetirom showed enhanced safety relative to T3 or other thyroid agonists. In animal models, resmetirom demonstrated cholesterol lowering, liver TG lowering, and reduction of markers of NASH-related liver inflammation and fibrosis at drug levels similar to those that lowered LDL-C in human clinical trials, providing data to support the advancement of resmetirom into NASH clinical trials. In chronic animal toxicology studies in dogs and rats, no effects on bone or cartilage histology were seen at any resmetirom dose in either species.

Resmetirom did not increase liver enzymes in Phase 1 studies and there were no bone and cartilage histologic findings in chronic animal toxicology studies.

Our Strategy

Our goal is to become a leading biopharmaceutical company developing and commercializing innovative liver-directed, ß-selective thyroid hormone receptor agonists for the treatment of cardio-metabolic and liver

disease, fibrosis and inflammation. A key element is building a multi-therapy NASH focused company. To achieve our goal, we plan to:

- ***Complete clinical development and seek regulatory approval of resmetirom in NASH.*** We successfully completed a Phase 2 clinical trial in NASH in 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 resmetirom is an excellent candidate for the chronic treatment of NASH due to its safety profile and first-in-class pleiotropic actions in liver cells and potential to reduce cardiovascular risk in NASH patients.
- ***Establish commercial capabilities to market resmetirom as a leading treatment for NASH.*** If approved, we intend to establish a sales and marketing organization with technical expertise and supporting distribution capabilities to commercialize resmetirom in the United States and through a biopharma partner in rest of the world. Patients with NASH and liver fibrosis are primarily managed by a concentrated group of NASH specialists in the United States. We believe this will enable us to launch resmetirom in NASH in a cost-effective, targeted manner, in the United States.
- ***Expand the resmetirom market opportunity to include patients with compensated NASH cirrhosis.*** Madrigal is conducting a Phase 3 trial – MAESTRO-NASH OUTCOMES – to noninvasively evaluate the effects of resmetirom on progression to liver decompensation events in NASH patients with compensated cirrhosis. A positive outcome is expected to support the full approval of resmetirom for noncirrhotic NASH, potentially accelerating the timeline to full approval. In addition, this study has the potential to support an additional indication for resmetirom in patients with well-compensated NASH cirrhosis.

Target Indications

Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

Overview and Market Opportunity

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. NASH and NAFLD have grown as a consequence of rising worldwide obesity-related disorders. In the United States, NAFLD is estimated to affect approximately 25% of the population, and approximately 25% of those will progress from NAFLD to NASH. Current estimates place NASH prevalence at approximately 22 million people in the United States by 2024, 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.

In addition to the accumulation of fat in the liver, NASH is characterized by inflammation and cellular damage with or without fibrosis, the first stage of liver scarring, which may ultimately progress to cirrhosis. Within NASH cirrhosis, patients can be categorized as being compensated or decompensated. NASH with compensated cirrhosis is characterized by liver scarring / damage that reduces the ability to process blood supplied to the liver, though patients generally remain asymptomatic with normal liver function. NASH patients with compensated cirrhosis are on the cusp of negative consequences associated with end-stage liver disease such as portal hypertension, esophageal varices, ascites, liver cancer and liver failure. It is estimated that by 2024 the prevalent cirrhotic NASH population in the US will be approximately 2.4 million with the vast majority of these patients (2.1 million) being categorized as compensated. The progression rate from compensated cirrhosis to decompensation, HCC, or death is ~20% over two years.

NASH is strongly associated with cardiovascular disease, or CVD, and the most common cause of death in NASH patients is CVD. Progression to cirrhosis and other late-stage complications can occur within five to ten years after an initial NASH diagnosis. NASH patients with type-2 diabetes have a heightened risk of NASH disease progression. Once the disease advances beyond NASH to such life-threatening conditions as liver cancer and liver failure, then liver transplantation is the only treatment alternative.

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 in the near future. 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.

Resmetirom Commercial Strategy

We have conducted quantitative and qualitative market research studies and secondary data analytics to inform the commercial strategy for resmetirom. These studies and analytics evaluated the size of the market opportunity for resmetirom as well as physician, patient and payer perspectives on unmet needs in NASH patient care and the resmetirom product profile.

Based on published epidemiology data and an analysis of medical claims using ICD-10 disease diagnosis codes, we believe that approximately one million NASH patients in the US have been coded with NASH as of 2021. Appropriate NASH patients with significant fibrosis within this group will be the initial focus of a potential resmetirom launch in the US. Over time, as disease awareness improves and disease prevalence increases, we expect the number of identified NASH patients with significant fibrosis eligible for treatment to grow meaningfully following the potential launch of resmetirom.

Our market research indicates the following. Key stakeholder audiences view NASH with significant fibrosis as an unmet medical need. **NASH specialist healthcare providers** (hepatologists, gastroenterologists, a subset of endocrinologists and affiliated advanced practice providers) who currently manage patients with NASH perceive the urgency to treat NASH with significant fibrosis to be similar to uncontrolled type 2 diabetes. In a market research survey, more than 70% of these healthcare providers indicated that they consider NASH with significant fibrosis to be a very high to extremely high unmet need. A separate survey found that **patients** perceive NASH as a priority condition, with approximately 60% ranking NASH as a priority over their other comorbidities. Patients reported low levels of satisfaction with current treatment options, and a majority of patients (~60%) strongly desire a new treatment for NASH. Market research interviews conducted with **payers** found that the vast majority of payers consider NASH with significant fibrosis to be a high unmet need given the lack of approved treatment options and that they intend to cover new product entrants for the treatment of patients with NASH. In market research conducted in Europe, payers indicated that the efficacy data demonstrated in our Phase 3 MAESTRO-NASH study may support reimbursement with key health technology assessment bodies in Europe similar to first-to-market products in disease categories with high unmet need.

In market research examining perceptions of the resmetirom product profile, U.S. physicians prioritized NASH resolution, fibrosis improvement, reduction in liver stiffness and improvement in cardiovascular/metabolic risk parameters as key profile attributes. Approximately 85% of physicians surveyed viewed the resmetirom product profile as offering high to extremely high clinical utility for the treatment of patients with NASH with significant fibrosis, with 40% of NASH specialists indicating anticipated use immediately at launch, if approved.

A key focus of our commercial strategy for the launch of resmetirom is educating physicians on the role of noninvasive tests for identifying patients who may be appropriate for resmetirom treatment and monitoring treatment response. Multiple medical societies, including the American Association for the Study of Liver Disease (AASLD), European Association for the Study of the Liver (EASL), American Gastroenterological Association (AGA), American Association of Clinical Endocrinologists and American Heart Association (AHA) have published guidance documents or scientific statements that provide community physicians with information

about the use of noninvasive tests to identify and manage patients with NASH. Our market research conducted in 2022 found that 80% of specialist healthcare providers managing patients with NASH in the U.S. have access to FibroScan, a noninvasive test that measures liver stiffness to estimate progression of fibrosis in patients with liver disease.

By 2030, we believe, including based on published research, that the prevalence of NASH patients with significant fibrosis (excluding NASH patients with compensated cirrhosis) will be approximately 19.1 million patients across the US, Germany, France, United Kingdom, Italy, Spain and Japan.

To evaluate the potential value and cost effectiveness of resmetirom as a treatment for NASH patients with significant liver fibrosis, we have initiated a series of health economics outcomes research studies and published a preliminary cost-effectiveness model (Javanbakht, Pharmacoecon Open, 2022) using data from the Phase 2 study of resmetirom. The cost-effectiveness model publication found that resmetirom is a potentially cost-effective treatment option for patients with NASH patients with significant liver fibrosis based on an analysis performed from a U.S. commercial payer perspective.

In the U.S., the Institute for Clinical and Economic Review ("ICER") performs value assessments of prescription drugs, medical tests, devices, and health system delivery innovations. Payers frequently review ICER reports when making coverage decisions about new therapies. In October 2022, ICER announced plans to perform a value assessment of resmetirom and obeticholic acid for the treatment of NASH. We have engaged in the assessment process by responding to data requests from ICER and providing public comment on ICER's cost-effectiveness modeling methods. In February 2023, a "Draft Evidence Report" was released with ICER's initial assessment of resmetirom cost-effectiveness. Threshold analyses were conducted by ICER to calculate the annual price needed to meet commonly accepted cost-effectiveness thresholds for quality-adjusted life years (QALY) gained. In ICER's draft assessment, the annual price to achieve $50,000 per QALY gained is $31,700. The annual price to achieve $100,000 per QALY gained is $39,400. The cost-effectiveness threshold analyses included in ICER's Draft Evidence Report are one input we will consider as we develop the pricing strategy for resmetirom. Other inputs include primary market research with payers and our health economics outcomes research. We plan to finalize and announce any U.S. pricing of resmetirom following approval.

We are tailoring our commercial strategy in the U.S. to support access and reimbursement for patients with different types of insurance coverage. Based on an analysis of claims data, we estimate that approximately 55% of patients with NASH in the U.S. have commercial insurance, 35% are insured through Medicare (half with the Medicare Part D Low Income Subsidy) and 10% through Medicaid. To support patient access and affordability, we intend to establish a specialty pharmacy network to distribute resmetirom and a patient services hub to help patients initiate and remain adherent to resmetirom therapy.

Based on market research and an assessment of the potential market opportunity for therapies to treat NASH with significant fibrosis, we have developed a commercial strategy for the launch of resmetirom that focuses on NASH specialist healthcare providers (hepatologists, gastroenterologists and a subset of endocrinologists) who already treat NASH patients with significant fibrosis. We estimate that there are 15,000 to 20,000 of these NASH specialists in the US. We believe that a specialty pharmaceutical sales force of up to 200 field sales representatives and account managers in the U.S. would be capable of reaching these healthcare providers during a launch of resmetirom. In addition to educating healthcare providers, we intend to launch direct-to-patient marketing efforts to improve awareness of NASH and resmetirom. Patient marketing initiatives will include unbranded NASH disease education resources prior to potential approval of resmetirom, followed by branded product advertising during the launch.

By 2030, we believe, including based on published studies, that the prevalence of NASH with compensated cirrhosis alone will be approximately 5.3 million patients across the US, Germany, France, United Kingdom, Italy, Spain and Japan. In market research, NASH specialists indicated that the unmet need in NASH with compensated cirrhosis is seen as higher than the unmet need in NASH with significant fibrosis because patients with compensated cirrhosis are closer to progressing to negative outcomes. Therefore, we believe that the

urgency to treat NASH patients with compensated cirrhosis will be high and resmetirom may be used in a larger proportion of NASH patients with compensated cirrhosis (relative to NASH patients with significant fibrosis).

By 2030, we believe, including based on published research, that the prevalence of NASH with significant fibrosis and NASH with compensated cirrhosis collectively will be approximately 24.4 million patients across the US, Germany, France, United Kingdom, Italy, Spain and Japan.

In 2022, we conducted market research examining physician perspectives on resmetirom's potential treatment profile for patients with compensated NASH cirrhosis. This research found that prescriber perceptions of efficacy and safety would improve if a medication were approved for use in patients with compensated NASH cirrhosis; more than 40% of physicians indicated that an approval for the NASH-compensated cirrhosis population would increase their willingness to prescribe for patients with significant fibrosis. Given that NASH patients with compensated cirrhosis require treatment from the same specialist physicians Madrigal is targeting for the launch of resmetirom in NASH with significant fibrosis, we anticipate that Madrigal will be able to support a potential expanded indication without a significant increase in the size of our commercial field force.

Over time, we believe primary care physicians will play a larger role in the management of patients with NASH, driven by factors that include improved disease awareness, uptake of noninvasive tests to screen and diagnose patients, and the growing global prevalence of NASH fueled by Western lifestyle.

We intend to commercialize resmetirom alone in the U.S. and to engage with a strategic partner or partners for commercializing resmetirom in all ex-U.S. territories.

We believe that the MAESTRO-NASH biopsy study results announced in December 2022 currently places resmetirom in a strong competitive position in Europe. In a draft reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases, the EMA indicated that conditional approval of NASH therapies in Europe may require achievement of two composite endpoints – (i) resolution of NASH with no worsening of the stage of fibrosis and (ii) improvement of fibrosis by at least one stage without any worsening of NASH – in a Phase 3 trial. The draft reflection paper states that "efficacy in these two composites should be demonstrated in co-primary fashion, meaning that both will have to independently demonstrate a statistically significant and clinically relevant difference to placebo." In the Phase 3 MAESTRO-NASH biopsy study, resmetirom achieved these composite endpoints.

Resmetirom in NASH

We are developing resmetirom for the treatment of non-cirrhotic NASH with fibrosis and NASH with compensated cirrhosis. Based on the scientific literature in human and animal studies, we believe that NASH livers in humans frequently have a deficiency in THR-ß activity that leads to features of NASH, including fatty liver, inflammation and fibrosis, and that treatment with resmetirom will replace this hormone deficiency and be an effective NASH treatment. We believe that resmetirom is an excellent candidate for the chronic treatment of NASH because of its safety and tolerability profile observed to date in healthy subjects, its effects in reducing cardiovascular risk factors such as LDL-C and TGs in early-stage clinical trials, and its multiple beneficial effects in animal models of NASH. CVD is the most common cause of death in patients with NASH. We have completed multiple studies in animal models of metabolic diseases, dyslipidemia and NASH in which resmetirom demonstrated a statistically significant reduction in liver TGs, insulin resistance, liver enzymes (which may be elevated in NASH), and markers of inflammation and fibrosis. We believe that resmetirom will treat the underlying lipotoxicity that drives the inflammation and liver cell damage observed in NASH patients, and after the underlying lipotoxicity is treated, NASH-related liver fibrosis will resolve as the liver regenerates.

Resmetirom NASH Phase 2 and 3 Clinical Studies

In October 2016, we initiated a Phase 2 proof of concept clinical trial in patients with liver biopsy documented NASH, including those with type-2 diabetes, dyslipidemia and hypertension. In the study we randomized 125

NASH patients 2:1, resmetirom or placebo QD in a double-blind, placebo-controlled, study of once-daily resmetirom versus placebo in patients with NASH, including those with type-2 diabetes. Patients continued treatment through 36 weeks. The study was conducted in the United States. The primary endpoint was to evaluate the efficacy of resmetirom as measured by the reduction of liver fat at 12 weeks, and the secondary endpoint was to evaluate the efficacy of resmetirom as measured by a reduction of NASH, which was assessed by liver biopsy, at 36 weeks. Other secondary and exploratory endpoints included safety and tolerability, and effects on serum biomarkers at 12 and 36 weeks, lipid parameters, and biomarker measures of insulin sensitivity. We reached our top-line analysis of the primary endpoint in December 2017, and we reached our top-line analysis of the secondary endpoint (NASH assessment on liver biopsy) in May 2018. There was an extension study in a subset of the patients that completed the main 36-week study which was completed in 2019. Madrigal has ongoing Phase 3 resmetirom studies for patients with NASH or presumed NASH as discussed in detail in this report.

We believe that the designs of our Phase 2 and Phase 3 NASH studies are consistent with principles for NASH drug development outlined by the FDA in its public communications and draft guidance for industry and based on our past interactions with FDA, including our end of Phase 2 meeting with the FDA in 2019.

Because of the slow progression of NASH and the time required to conduct an outcomes trial that would evaluate clinical endpoints such as progression to cirrhosis or survival, the FDA recommends sponsors consider the following liver histological improvements as Phase 3 trial endpoints reasonably likely to predict clinical benefit to support accelerated approval under subpart H regulations:

Resolution of steatohepatitis on overall histopathological reading and no worsening of liver fibrosis;

Or

Improvement in liver fibrosis greater than or equal to one stage and no worsening of steatohepatitis;

Or

Both resolution of steatohepatitis and improvement in fibrosis.

In March 2019, the Company announced that it had initiated MAESTRO-NASH, a Phase 3 trial of resmetirom in patients with NASH. MAESTRO-NASH is a multicenter, randomized, double-blind, placebo-controlled Phase 3 study of resmetirom in patients with liver biopsy-confirmed NASH and was initiated in March 2019. The subpart H portion of the study enrolled more than 1,000 patients with biopsy-proven NASH (at least half with F3 (advanced) fibrosis, the remainder F2 or F1B (moderate fibrosis) with a few earlier F1 patients), randomized 1:1:1 to receive once-daily resmetirom 80 mg, resmetirom 100 mg, or placebo. After 52 weeks of treatment, a second liver biopsy is performed. The dual primary surrogate endpoints on biopsy are NASH resolution with ≥2-point reduction in NAS (NAFLD Activity Score), and with no worsening of fibrosis OR a 1-point decrease in fibrosis with no worsening of NAS. Achievement of either primary endpoint is considered a successful trial outcome. A key secondary endpoint is lowering of LDL-C.

All patients enrolled in the MAESTRO-NASH study (up to 2,000 in total) continue on therapy after the initial 52-week treatment period for up to 54 months to accrue and measure hepatic clinical outcome events including progression to cirrhosis on biopsy (52 weeks and 54 months) and hepatic decompensation events, as well as all-cause mortality.

In December 2022, we reported topline results from the subpart H portion of the study: resmetirom achieved both primary endpoints with both daily oral doses, 80 mg and 100 mg, relative to placebo, as summarized in “- Key Developments” above.

In December 2019 the Company announced it had opened for enrollment MAESTRO-NAFLD-1, a 52-week, double-blind, placebo controlled Phase 3 clinical study in 700 patients with biopsy-confirmed or

presumed NASH recruited from sites in the U.S. Key endpoints are safety, including safety biomarkers, LDL cholesterol, lipid biomarkers, and fibrosis biomarkers. Except for serial liver biopsies, the study protocol is similar to the MAESTRO-NASH study with resmetirom doses of 80 mg or 100 mg or placebo and includes key secondary lipid, MRI-PDFF and NASH biomarker endpoints. In addition, MAESTRO-NAFLD-1 includes an open label arm in which up to 100 patients will be dosed with 100 mg resmetirom. Enrollment objectives for this study have been exceeded, with approximately 1,200 patients enrolled overall. In October 2020 we completed enrollment of the double-blind, placebo controlled arms of the study. The MAESTRO-NAFLD-1 study will help support the adequacy of the safety database at the time of NDA submission for subpart H approval or treatment of NASH in patients with F2 or F3 fibrosis.

MAESTRO-NAFLD-1 also includes an open label arm with approximately 170 non-cirrhotic patients with NASH treated with 100 mg resmetirom. Data from this open label portion of the MAESTRO-NAFLD-1 study have been reported at various professional society conferences, demonstrating statistically significant reductions from baseline in liver fat as assessed by MRI-PDFF and Fibroscan CAP, as well as reductions in liver stiffness as determined by MRE and Fibroscan TE (a surrogate for liver fibrosis). Markers of liver fibrosis and inflammation were also reduced by resmetirom relative to baseline. Additionally, atherogenic lipids, including LDL-cholesterol, apolipoprotein B, triglycerides, and lipoprotein (a) were reduced relative to baseline. The adverse event profile in this open label cohort has been similar to that observed in Phase 2. The MAESTRO-NAFLD-1 open label arm over-enrolled and includes more than 150 patients with NASH and compensated cirrhosis to obtain a preliminary assessment of the use of resmetirom in patients with more advanced disease.

In January 2022, Madrigal announced topline results from the Phase 3 MAESTRO-NAFLD-1 safety study of resmetirom. Primary and key secondary endpoints from the double-blind placebo-controlled 969-patient portion of the study were achieved, as described herein. See " – Key Developments" above.

Collaborations

VIA Pharmaceuticals, Inc., or VIA, entered into a research, development and commercialization agreement, or the Roche Agreement, with Roche, on December 18, 2008. We subsequently assumed all of VIA's rights in, to and under, and all of VIA's obligations under, the Roche Agreement pursuant to an asset purchase agreement, dated September 14, 2011. Pursuant to the terms of the Roche Agreement, we, as successor-in-interest to VIA, assumed control of all development and commercialization of resmetirom and will hold exclusive worldwide rights for all potential indications. Under the Roche Agreement, Roche exclusively licensed certain patent rights and know-how relating to resmetirom in exchange for consideration consisting of an upfront payment, milestone payments, the remainder of which total $8 million and are tied to regulatory approval in the United States and Europe of resmetirom or any derivative product, and single-digit royalty payments based on net sales of resmetirom and any derivative products, subject to certain reductions. In 2011, we commenced Phase 1 clinical trials and subsequently paid Roche a related milestone payment. In October 2016, we commenced a Phase 2 study in NASH and subsequently paid Roche a related milestone payment. In 2019, we commenced a Phase 3 study in NASH and subsequently paid Roche a $2 million related milestone payment. Except as described above, we have not achieved any additional product development or regulatory milestones under the Roche Agreement and have generated no net sales of products developed from resmetirom.

Pursuant to the Roche Agreement, we must use commercially reasonable efforts to conduct clinical and commercial development programs for products containing resmetirom. If we determine that it is not reasonable to continue clinical trials or other development of resmetirom, we may elect to cease further development and Roche may terminate the license. If we determine not to pursue the development or commercialization of resmetirom 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 of the agreement, 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 resmetirom, or (ii) ten years after the first sale of a product containing resmetirom.

Competition

The development and commercialization of new drugs is highly competitive. We will face competition with respect to all product candidates we may develop or commercialize in the future from pharmaceutical and biotechnology companies worldwide. The key factors affecting the success of any approved product will be its efficacy, safety profile, drug interactions, method of administration, pricing, reimbursement and level of promotional activity relative to those of competing drugs.

- Our potential competitors may have substantially greater financial, technical, and personnel resources than us. In addition, many of these competitors have significantly greater commercial infrastructures. Our ability to compete successfully will depend largely on our ability to leverage our collective experience in drug discovery, development and commercialization to:
- discover and develop medicines that are differentiated from other products in the market,
- obtain patent and/or proprietary protection for our products and technologies;
- obtain required regulatory approvals;
- obtain a commercial partner;
- commercialize our drugs, if approved; and
- attract and retain high-quality research, development and commercial personnel.

There are currently no therapeutic products approved and marketed for the treatment of NASH in North America and Europe. There are several commercially available products that are currently used off-label for NASH, such as vitamin E, an antioxidant, insulin sensitizers, such as pioglitazone, anti-hyperlipidemic agents, such as gemfibrozil, pentoxifylline, ursodiol and others. In addition, there are numerous drugs in development for the treatment of NASH. We are aware of several companies that have product candidates in clinical development for the treatment of NASH, including Intercept Pharmaceuticals, Inc., Gilead Sciences, Inc., Galectin Therapeutics, Inc., Galmed Medical Research Ltd., Cirius Therapeutics, Novartis AG, Novo Nordisk A/S, Takeda, Inventiva, Boehringer Ingelheim GmbH, Bristol-Myers Squibb, Pfizer, Inc., Merck & Co., Lilly, Genentech, Sanofi S.A., NGM Biopharmaceutical, Viking Therapeutics, Akero Therapeutics, Enanta Pharmaceuticals, 89Bio Inc., Axcella, Can-Fite, Hepion, NorthSea, Terns, Zydus Cadila and MedImmune LLC, Altimune, Poxel, Ascletis Pharma, and there are other companies with candidates in earlier stages of development. Given resmetirom's actions on the underlying biological pathways across the spectrum of early to late stages of NASH, its CV beneficial effects, and its complementary mechanism to other therapies, we believe that resmetirom has the potential to be used alone or in combination with some of these potential NASH products.

Glucagon-like peptide 1 (GLP-1) agonists play an increasing role in the management of patients with diabetes and obesity, and are being studied for the treatment of NASH in Phase 2 and Phase 3 trials. Based on analysis of claims data, Madrigal estimates that approximately 6% of ICD-10 coded patients with NASH in the U.S. are currently being treated with GLP-1 agonists for any indication. As of the date of this filing, there have been no successful Phase 3 trials evaluating a GLP-1 agonist for the treatment of NASH. Madrigal believes that resmetirom should have a competitive advantage based on its liver-directed efficacy, tolerability profile and once-daily oral dosing. Madrigal anticipates that combination therapy with resmetirom and GLP-1 agonists may be used to manage NASH patients with significant fibrosis and comorbiditis such as diabetes or obesity Madrigal believes the introduction of GLP-1 medications for the treatment of NASH should not have a material adverse effect on market potential of resmetirom, if approved.

Sales and Marketing

Madrigal has established a commercial leadership team with expertise in launching pharmaceutical products. As of the date of this filing, Madrigal has no field sales team and no product distribution capabilities. As resmetirom nears potential accelerated approval in the U.S., we intend to expand our marketing organization, establish a sales organization, and build distribution capabilities to commercialize resmetirom.

Manufacturing

We do not own or operate, and currently have no plans to establish, any manufacturing facilities. We currently rely, and expect to rely, on third-party contract manufacturers, or CMOs, for all required starting materials, API and finished product for the manufacture of any product candidates that we may develop for larger-scale preclinical and clinical testing, as well as for commercial quantities of any drug candidates that are approved. We do not have long-term supply agreements for any of our product candidates and regularly obtain supplies and services related to our product candidates from CMO's on a purchase order basis. We currently have a single source for API and finished product for resmetirom and are developing a second source for API. We plan to continue to rely on CMOs for API, finished product, packaging, storage, and distribution for both clinical supplies and any of our product candidates that receive health authority approval.

Research and Development

Research and development expenses primarily consist of costs associated with our research activities, including the preclinical and clinical development of our product candidates. Our research and development expenses were $245.4 million for the year ended December 31, 2022, $205.2 million for the year ended December 31, 2021, and $184.8 million for year ended December 31, 2020. The increase in research and development expenses was primarily due to the advancement of clinical programs to Phase 3 studies, further API manufacturing studies and the continuation of preclinical studies. We expect research and development expenses to increase over time as we advance our clinical and preclinical development programs for resmetirom.

Intellectual Property

We will be able to protect our technology and products from unauthorized use by third parties only to the extent we are covered by valid and enforceable patents or such knowledge is effectively maintained as trade secrets. Patents and other proprietary rights are thus an essential element of our business. We also rely on trade secrets, know-how, continuing technological innovation and licensing opportunities to develop and maintain our competitive position.

Our success will depend in part on our ability to obtain and maintain patent and other proprietary protection for our current and future product candidates, technology and know-how, to operate without infringing on the proprietary rights of others, and to prevent others from infringing our proprietary rights. We seek to protect our proprietary position by, among other methods, filing United States and foreign patent applications related to our proprietary technology, and maintaining the confidentiality of inventions and improvements that are important to the development of our business.

As of December 7, 2022, we own or co-own: five United States and 38 foreign issued patents; five United States and 43 foreign pending patent applications; and three international patent applications filed under the Patent Cooperation Treaty. Each of these patents and applications relates to resmetirom, including composition-of-matter, certain dosage forms, methods of making resmetirom, its use in the treatment of key disease indications, or other THR beta analogs and uses thereof. Our current patent portfolio covers the United States and certain other jurisdictions worldwide. The three international patent applications can be used as the basis for multiple additional patent applications worldwide. In addition, pursuant to the Roche Agreement, Roche granted us an exclusive license to certain United States and foreign patents and patent applications owned by Roche and Roche know-how relating to resmetirom. The Roche Agreement imposes various diligence, milestone payment, royalty payment, insurance, indemnification, and other obligations on us.

Issued patents directed to resmetirom, including certain dosage forms, have statutory expiration dates between 2026 and 2037, excluding any patent term extensions or equivalents thereof that might be available following the grant of marketing authorizations. We have pending patent applications for resmetirom that, if issued, would be expected to expire in the United States and in countries outside of the United States between 2033 and 2042, excluding any patent term adjustment that might be available following the grant of the patent and any patent term extensions that might be available following the grant of marketing authorizations. We have

a pending patent application for other THR beta analogs that, if issued, would be expected to expire in the United States and in countries outside of the United States in 2043, excluding any patent term adjustment that might be available following the grant of the patent and any patent term extensions that might be available following the grant of marketing authorizations.

Our trademarks are protected under the common law and/or by registration in the United States and other countries. We seek to protect our proprietary processes, in part, by confidentiality agreements and invention assignment agreements with our personnel, including consultants and commercial partners. These agreements are designed to protect our proprietary information.

Orphan Drug Designation

Some potential target disease indications for resmetirom are rare diseases or may be designated rare diseases and we plan to pursue orphan drug designation where possible. If granted, each such designation might provide for regulatory exclusivity for seven years in the United States and ten years in the EU from the date of product approval for individual indications.

Government Regulation

Government Regulation and Product Approval

Government authorities in the United States, at the federal, state and local level, and other countries extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, monitoring and reporting, promotion, advertising, distribution, marketing and export and import of drug products such as those we are developing. A new drug must be approved by the FDA through the new drug application, or NDA, process before it may be legally marketed in the United States, and must be approved by foreign regulatory authorities via various analogous procedures before it can be marketed in the applicable country. The animal and other non-clinical data and the results of human clinical trials performed under an Investigational New Drug application, or IND, and under similar foreign applications will become part of the NDA.

United States Drug Development Process

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state and local statutes and regulations require the expenditure of substantial time and financial resources. Failure to comply with the applicable United States requirements at any time during the product development process, approval process or after approval, may subject an applicant to administrative or judicial sanctions. These sanctions could include, among other things, the FDA's refusal to approve pending applications, withdrawal of an approval, a clinical hold, warning letters and other types of enforcement-related letters, requesting product recalls, product seizures, changes to the conditions surrounding marketing approval such as labeling changes or changes to a Risk Evaluation and Mitigations Strategies, or REMS, program, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, debarment, restitution, disgorgement of profits, or civil or criminal investigations and penalties. Any agency or judicial enforcement action could have a material adverse effect on us. The process required by the FDA before a drug or biologic may be marketed in the United States generally involves the following:

- completion of preclinical laboratory tests, animal studies and formulation studies, some in accordance with the FDA's current Good Laboratory Practices, or GLP, the Animal Welfare Act administered and enforced by the United States Department of Agriculture, and other applicable regulations;
- submission to the FDA of an IND which must become effective before human clinical trials may begin;

- approval by an institutional review board, or IRB, before each trial may be initiated at each clinical site;
- performance of adequate and well-controlled human clinical trials under protocols submitted to the FDA and reviewed and approved by each IRB, conducted in accordance with federal regulations and according to Good Clinical Practices, or GCP, to establish the safety and efficacy of the proposed drug for its intended use;
- submission to the FDA of an NDA;
- completion of registration batches and validation of the manufacturing process to show ability to consistently produce quality batches of product;
- satisfactory completion of an FDA Advisory Committee review, if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the drug is produced to assess compliance with current good manufacturing practice, or cGMP, to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity; and
- FDA review and approval of the NDA.

Once a pharmaceutical candidate is identified for development, it enters the preclinical testing stage. Preclinical tests include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies, to assess the safety and quality of the product. Animal studies must be performed in compliance with federal regulations and requirements, including, as applicable, GLP and the Animal Welfare Act. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information and analytical data, to the FDA as part of the IND. The sponsor will also include a protocol detailing, among other things, the objectives of the clinical trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated, if the trial lends itself to an efficacy evaluation. Some preclinical testing may continue even after the IND is submitted. A 30-day waiting period after the submission of each IND is required prior to the commencement of clinical testing in humans. If during this 30-day period the FDA does not raise any concerns or issues that must be addressed prior to the commencement of clinical trials or does not impose a clinical hold, the IND becomes effective 30 days following the FDA's receipt of the IND and the clinical trial proposed in the IND may begin. Clinical holds also may be imposed by the FDA at any time before or during studies due to safety concerns or non-compliance, or other reasons.

All clinical trials must be conducted under the supervision of one or more qualified investigators in accordance with GCP. They must be conducted under protocols detailing the objectives of the trial, dosing procedures, subject selection and exclusion criteria and the safety and effectiveness criteria to be evaluated. Each protocol must be submitted to the FDA as part of the IND, and progress reports detailing the results of the clinical trials must be submitted at least annually. In addition, timely safety reports must be submitted to the FDA and the investigators for serious and unexpected adverse events or animal test results that suggest a significant risk to human subjects. An IRB at each institution participating in the clinical trial must review and approve each protocol before a clinical trial commences at that institution and must also approve the information regarding the trial and the consent form that must be provided to each trial subject or his or her legal representative, monitor the study until completed and otherwise comply with IRB regulations. Foreign studies conducted under an IND must meet the same requirements that apply to studies being conducted in the U.S. Data from a foreign study not conducted under an IND may be submitted in support of an NDA if the study was conducted in accordance with GCP and the FDA is able to validate the data.

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

- *Phase 1:* The product candidate is initially introduced into humans. Phase 1 clinical trials are typically conducted in healthy human subjects, but in some situations are conducted in patients with the target disease or condition. Phase 1 clinical trials are generally designed to evaluate the

safety, dosage tolerance, absorption, metabolism, distribution and excretion of the product candidate in humans, and, if possible, to gain early evidence of effectiveness.

- *Phase 2:* This phase involves studies in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product candidate for specific targeted diseases and to determine dosage tolerance and optimal dosage.
- *Phase 3:* This phase involves trials undertaken to further evaluate dosage, clinical efficacy and safety in an expanded patient population at geographically dispersed clinical study sites. These studies are intended to establish the overall risk-benefit ratio of the product candidate and provide, if appropriate, an adequate basis for product approval and product labeling. In most cases, the FDA requires two adequate and well controlled Phase 3 clinical trials to demonstrate the efficacy of the product candidate, although a single Phase 3 clinical trial with other confirmatory evidence may be sufficient in certain instances.

The FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. Phase 1, Phase 2, and Phase 3 testing may not be completed successfully within any specified period, if at all. Further, success in either preclinical studies or early-stage clinical trials does not assure success in later-stage clinical trials. Sponsors of all controlled clinical trials, except for Phase 1 trials, are required to submit certain clinical trial information for inclusion in the public clinical trial registry and results data bank maintained by the National Institutes of Health, which are publicly available at http://clinicaltrials.gov.

During the development of a new drug, sponsors are given opportunities to meet with the FDA at certain points. These points may be prior to submission of an IND, at the end of Phase 2, and before an NDA is submitted. Meetings at other times may be requested. These meetings can provide an opportunity for the sponsor to share information about the data gathered to date, for the FDA to provide advice, and for the sponsor and FDA to reach agreement on the next phase of development. Sponsors typically use the end of Phase 2 meeting to discuss their Phase 2 clinical results and present their plans for the pivotal Phase 3 clinical trial that they believe will support approval of the new drug.

Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug and finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final drug. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

United States Review and Approval Processes

The results of product development, preclinical studies and clinical trials, along with descriptions of the manufacturing process, analytical tests conducted on the chemistry of the drug, proposed labeling, and other relevant information are submitted to the FDA as part of an NDA requesting approval to market the product for a specific indication. The submission of an NDA is subject to the payment of user fees under the Prescription Drug User Fee Act, or PDUFA, as amended; a waiver of such fees may be obtained under certain limited circumstances. The FDA conducts a preliminary review of a submitted NDA within 60 days from receipt to ensure that the application is sufficiently complete for substantive review before it accepts the application for filing. The FDA may request additional information rather than accept an NDA for filing. In this event, the NDA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA's PDUFA performance goals generally provide for action on an NDA within 10 months of the

60-day filing date. That deadline can be extended under certain circumstances, including by the FDA's requests for additional information. The targeted action date can also be shortened to within 6 months of the 60-day filing date for products that are granted priority review designation because they are intended to treat serious or life-threatening conditions and demonstrate the potential to address unmet medical needs. The FDA reviews an NDA to determine, among other things, whether a product is safe and effective for its intended use and whether its manufacturing is cGMP-compliant to assure and preserve the product's identity, strength, quality and purity. Before approving an NDA, the FDA will inspect the facility or facilities where the product is manufactured. In addition, the FDA often will conduct a bioresearch monitoring inspection of the clinical trial sites involved in conducting pivotal studies to ensure data integrity and compliance with applicable GCP requirements. The FDA may refer the NDA to an advisory committee for review, evaluation and recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations. The approval process is lengthy and often difficult, and the FDA may refuse to approve an NDA if the applicable regulatory criteria are not satisfied or may require additional clinical or other data and information. Even if such data and information are submitted, the FDA may ultimately decide that the NDA does not satisfy the regulatory criteria for approval. Data obtained from clinical trials are not always conclusive, and the FDA may interpret data differently than we interpret the same data.

At the end of the review period, the FDA may issue an approval letter following satisfactory completion of all aspects of the review process, or the FDA may issue a complete response letter, or CRL, which generally outlines the deficiencies in the submission and may require additional clinical or other data or impose other conditions that must be met in order to secure final approval of the NDA. If and when deficiencies outlined in a CRL have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA may issue an approval letter. The FDA's PDUFA review goal is to review such resubmissions within two or six months of receipt, depending on the type of information included. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval and deny approval of a resubmitted NDA.

NDAs receive either standard or priority review. An application for a drug that treats a serious condition and, if approved, would provide a significant improvement in treatment, prevention or diagnosis of disease may qualify for priority review. Priority review for an NDA for a new molecular entity will be six months from the date that the NDA is filed. The FDA has ten months in which to complete its initial review of a standard new molecular entity NDA. The FDA does not always meet its goal dates and in certain circumstances the goal date may be extended. Priority review does not change the standard for approval, but may expedite the approval process.

Product candidates may qualify for review and approval under the subpart H-accelerated approval pathway if the candidates are intended to treat a serious condition, provide meaningful therapeutic benefit over existing treatments, and demonstrate an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on an intermediate clinical endpoint. In clinical trials, a surrogate endpoint is a measurement of laboratory or clinical signs of a disease or condition that substitutes for a direct measurement of how a patient feels, functions, or survives. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. As a condition of accelerated approval, the FDA requires that a sponsor of a drug receiving accelerated approval perform confirmatory adequate and well-controlled post-marketing clinical trials. Accelerated approval does not change the standards for approval. All promotional materials for drug candidates approved under the accelerated approval pathway are subject to prior review by the FDA. If a sponsor fails to conduct any required post-approval trial with "due diligence" FDA may withdraw the drug from the market.

Further, on December 29, 2022, Congress enacted the Consolidated Appropriations Act of 2023, which included the Food and Drug Omnibus Reform Act (FDORA). Under FDORA, FDA must specify the conditions for any post-approval studies by the date of the accelerated approval and gives the agency much flexibility in setting forth such conditions, which may include enrollment targets, study protocol and milestones – including the target date of study completion. FDA may also require, as appropriate, that certain post-approval studies be

underway prior to accelerated approval or within a specified time from the date of approval. Accelerated approval sponsors must submit progress reports every six months on required post-approval trials.

An approval letter authorizes commercial marketing of the product candidate with specific prescribing information for specific indications. If a product receives regulatory approval, the approval may be further limited to specific diseases, dosages or patient populations, or the indications for use may otherwise be limited, which could restrict the commercial value of the product. In addition, the FDA may require a sponsor to conduct Phase 4 testing which involves clinical trials designed to further assess a drug's safety and effectiveness after NDA approval, and may require testing and surveillance programs to monitor the safety of approved products which have been commercialized.

The Food and Drug Administration Safety and Innovation Act, or FDASIA, which was enacted in 2012, made permanent the Pediatric Research Equity Act, or PREA, which requires a sponsor to conduct pediatric studies for most drugs and biologics, for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration. Under PREA, original NDAs and supplements thereto must contain a pediatric assessment unless the sponsor has received a deferral or waiver. The required assessment must assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations and support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The sponsor or FDA may request a deferral of pediatric studies for some or all of the pediatric subpopulations. A deferral may be granted for several reasons, including a finding that the drug or biologic is ready for approval for use in adults before pediatric studies are complete or that additional safety or effectiveness data needs to be collected before the pediatric studies begin. The FDA must send a non-compliance letter to any sponsor that fails to submit the required assessment, keep a deferral current or fails to submit a request for approval of a pediatric formulation.

Patent Term Restoration and Regulatory Exclusivities

Depending upon the timing, duration and specifics of FDA approval of our product candidates, some of our United States patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Act. The Hatch-Waxman Act permits a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND, and the submission date of an NDA, plus the time between the submission date of an NDA and the approval of that application, except that the period is reduced by any time during which the applicant failed to exercise due diligence. Only one patent applicable to an approved drug is eligible for the extension, and the extension must be applied for prior to expiration of the patent and within 60 days of approval. The United States Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration.

The Hatch-Waxman Act also provides periods of regulatory exclusivity for products that would serve as a reference listed drug, or RLD, for an abbreviated new drug application, or ANDA, or application submitted under section 505(b)(2) of the FDCA, or 505(b)(2) application. If a product is a new chemical entity, or NCE—generally meaning that the active moiety has never before been approved in any drug—there is a period of five years from the product's approval during which the FDA may not accept for filing any ANDA or 505(b)(2) application for a drug with the same active moiety. An ANDA or 505(b)(2) application may be submitted after four years, however, if the sponsor of the application makes a "Paragraph IV" certification.

A product that is not an NCE may qualify for a three-year period of exclusivity if the NDA contains new clinical data (other than bioavailability studies), derived from studies conducted by or for the sponsor, that were necessary for approval. In that instance, the exclusivity period does not preclude filing or review of an ANDA or 505(b)(2) application; rather, the FDA is precluded from granting final approval to the ANDA or 505(b)(2)

application until three years after approval of the RLD. Additionally, the exclusivity applies only to the conditions of approval that required submission of the clinical data.

Once the FDA accepts for filing an ANDA or 505(b)(2) application containing a Paragraph IV certification, the applicant must within 20 days provide notice to the RLD NDA holder and patent owner that the application has been submitted and provide the factual and legal basis for the applicant's assertion that the patent is invalid or not infringed. If the NDA holder or patent owner files suit against the ANDA or 505(b)(2) applicant for patent infringement within 45 days of receiving the Paragraph IV notice, the FDA is prohibited from approving the ANDA or 505(b)(2) application for a period of 30 months or the resolution of the underlying suit, whichever is earlier. If the RLD has NCE exclusivity and the notice is given and suit filed during the fifth year of exclusivity, the regulatory stay extends until seven and a half years after the RLD approval. The FDA may approve the proposed product before the expiration of the regulatory stay if a court finds the patent invalid or not infringed or if the court shortens the period because the parties have failed to cooperate in expediting the litigation.

Pediatric exclusivity is another type of marketing exclusivity available in the United States. The FDASIA made permanent the Best Pharmaceuticals for Children Act, or BPCA, which provides for an additional six months of marketing exclusivity if a sponsor conducts clinical trials in children in response to a written request from the FDA, or a Written Request. If the Written Request does not include studies in neonates, the FDA is required to include its rationale for not requesting those studies. The FDA may request studies on approved or unapproved indications in separate Written Requests. The issuance of a Written Request does not require the sponsor to undertake the described studies.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan drug designation to a drug or biological product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for this type of disease or condition will be recovered from sales in the United States for that drug. Orphan drug designation must be requested before submitting an NDA. After the FDA grants orphan drug designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in or shorten the duration of the regulatory review and approval process. 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 product exclusivity, which means that the FDA may not approve any other applications to market the same drug for the same indication, except in very limited circumstances, for seven years. Orphan drug exclusivity, however, also could block the approval of one of our product candidates for seven years if a competitor obtains approval of the same drug as defined by the FDA or if our product candidate is determined to be contained within the competitor's product for the same indication or disease.

The FDA also administers an orphan drug clinical research grants program, whereby researchers may apply for funding to conduct clinical trials to support the approval of drugs, biologics, medical devices, and medical foods for rare diseases and conditions. A product does not have to be designated as an orphan drug to be eligible for the grant program. An application for an orphan grant should propose one discrete clinical study to facilitate FDA approval of the product for a rare disease or condition. The study may address an unapproved new product or an unapproved new use for a product already on the market.

Expedited Programs

The FDA maintains several programs to facilitate and expedite the development and review of drug applications that are intended for the treatment of a serious or life-threatening disease or condition for which there is no effective treatment and that demonstrate the potential to address unmet medical needs for such a

disease or condition, including Fast Track Designation, Breakthrough Designation, Priority Review (discussed above in United States Review and Approval Processes), and the Accelerated Approval pathway (discussed above in United States Review and Approval Processes). Under the Fast Track Designation program, the sponsor of a new drug candidate may request that the FDA designate the drug candidate for a specific indication as a fast track drug concurrent with, or after, the filing of the IND for the drug candidate. The FDA must determine if the drug candidate qualifies for fast track designation within 60 days of receipt of the sponsor's request. Under the Fast Track Designation program, the FDA may grant fast track designation for a product candidate if it is intended to treat a serious or life-threatening condition and nonclinical or clinical data demonstrate the potential to address an unmet medical need. Features of Fast Track Designation include more frequent interactions with the review team, and the possibility of rolling review.

Under the Breakthrough Designation Program, FDA may grant a drug Breakthrough Therapy Designation if it is intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint over available therapies. Features of Breakthrough Therapy Designation include intensive guidance on an efficient drug development program, an organizational commitment by the agency involving senior managers in a proactive, cross-disciplinary review of the drug application, and the possibility of rolling review.

Post-Approval Requirements

Once an approval is granted, products are subject to continuing regulation by the FDA. The FDA may withdraw the approval if, among other things, compliance with regulatory standards is not maintained or if safety or efficacy problems occur after the product reaches the market. Later discovery of previously unknown problems with a product may result in restrictions on product marketing or even withdrawal of approval for the product application. If new safety issues are identified following approval, the FDA may require the NDA sponsor to take certain measures, such as revising the approved labeling to reflect the new safety information, conducting post-market studies or clinical trials to assess the new safety information, and/or implementing or changing a risk evaluation and mitigation strategy, or REMS, program to mitigate newly-identified risks. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further FDA review and approval. Drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP and other laws and regulations. We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our product candidates. Future inspections by the FDA and other regulatory agencies may identify compliance issues at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct.

Any drug products manufactured or distributed by us pursuant to FDA approvals are subject to continuing regulation by the FDA, including, among other things, record-keeping requirements, reporting of adverse experiences with the drug, providing the FDA with updated safety and efficacy information, drug sampling and distribution requirements, complying with certain electronic records and signature requirements, and complying with FDA promotion and advertising requirements. The FDA strictly regulates labeling, advertising, promotion and other types of information on products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label.

From time to time, legislation is drafted, introduced and passed in Congress that could significantly change the statutory provisions governing the approval, manufacturing and marketing of products regulated by the FDA. In addition to new legislation, FDA regulations and guidance are often revised or interpreted by the agency in ways that may significantly affect our business and our products. It is impossible to predict whether further legislative changes will be enacted, or FDA regulations, guidance or interpretations changed or what the impact of such changes, if any, may be.

Foreign Regulation

In addition to regulations in the United States, we will be subject to a variety of foreign regulations governing clinical trials and commercial sales and distribution of its products. Whether or not we obtain FDA approval for a product, we must obtain approval by the comparable regulatory authorities of foreign countries or economic areas, such as the European Union, before we may commence clinical trials or market products in those countries or areas. The approval process and requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from place to place, and the time may be longer or shorter than that required for FDA approval.

Under EU regulatory systems, a company may submit marketing authorization applications either under a centralized or decentralized procedure. The centralized procedure, which is compulsory for medicinal products produced by biotechnology or those medicinal products containing new active substances for specific indications such as the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, viral diseases and designated orphan medicines, and optional for other medicines which are highly innovative. Under the centralized procedure, a marketing application is submitted to the EMA where it will be evaluated by the Committee for Medicinal Products for Human Use and a favorable opinion typically results in the grant by the European Commission of a single marketing authorization that is valid for all EU member states within 67 days of receipt of the opinion. The initial marketing authorization is valid for five years, but once renewed is usually valid for an unlimited period. The decentralized procedure provides for approval by one or more "concerned" member states based on an assessment of an application performed by one member state, known as the "reference" member state. Under the decentralized approval procedure, an applicant submits an application, or dossier, and related materials to the reference member state and concerned member states. The reference member state prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. Within 90 days of receiving the reference member state's assessment report, each concerned member state must decide whether to approve the assessment report and related materials. If a member state does not recognize the marketing authorization, the disputed points are eventually referred to the European Commission, whose decision is binding on all member states. In addition to the centralized procedure and the decentralized procedure, it may also be possible to obtain a marketing authorization for one single EU Member State through a national procedure. Under a mutual recognition procedure, a national marketing authorization granted by one EU Member State may be recognized by one or more other EU Member States resulting in harmonized marketing authorizations in those EU Member States.

When conducting clinical trials in the EU, we must adhere to the provisions of the EU Clinical Trials Directive and the laws and regulations of the EU Member States implementing them. These provisions require, among other things, that the prior authorization of an Ethics Committee and the submission and approval of a clinical trial authorization application be obtained in each Member State before commencing a clinical trial in that Member State. On January 31, 2022, the EU Clinical Trials Regulation (EU) No 536/2014 (Clinical Trials Regulation) came into effect. The Clinical Trials Regulation applies to clinical trials in all countries of the European Economic Area (EEA, i.e., the EU Member States plus Iceland, Norway and Liechtenstein). The Clinical Trials Regulation allows investigators to start and conduct a clinical trial in accordance with the Clinical Trials Directive during a transitional period of one year after the application date (i.e., January 31, 2022). Clinical trials authorized under the Clinical Trials Directive before January 31, 2023 can continue to be conducted under the Clinical Trials Directive until January 31, 2025. An application to transition ongoing trials from the current Clinical Trials Directive to the new Clinical Trials Regulation will need to be submitted and authorized in time before the end of the transitional period. The EU Clinical Trials Regulation introduces a complete overhaul of the existing regulation of clinical trials for medicinal products in the EU, including a new coordinated procedure for authorization of clinical trials that is similar to the mutual recognition procedure for marketing authorization of medicinal products, and increased obligations on sponsors to publish clinical trial results.

As in the United States, it may be possible in foreign countries to obtain a period of market and/or data exclusivity that would have the effect of postponing the entry into the marketplace of a competitor's generic product. For example, in the EU, if any of our products receive marketing approval in the European Economic Area, or EEA, which is comprised of the 27 member states of the EU plus Norway, Iceland and Liechtenstein, we expect that we will benefit from eight years of data exclusivity and an additional two years of marketing exclusivity. An additional one-year extension of marketing exclusivity is possible if during the data exclusivity period we obtain an authorization for one or more new therapeutic indications that is deemed to bring a significant clinical benefit compared to existing therapies. The data exclusivity period begins on the date of the product's first marketing authorization in the EU and prevents biosimilars from relying on the holder of the marketing authorization for the reference biological medicine's pharmacological, toxicological and clinical data for a period of eight years. After eight years, a biosimilar product application may be submitted and the sponsoring companies may rely on the marketing authorization holder's data. However, a biosimilar medicine cannot launch until 2 years later (or a total of ten years after the first marketing authorization in the EU of the innovator product), or 3 years later (or a total of eleven years after the first marketing authorization in the EU of the innovator product) if the marketing authorization holder obtains marketing authorization for a new indication with significant clinical benefit within the eight year data exclusivity period.

As in the United States, a sponsor may apply for designation of a product as an orphan drug for the treatment of a specific indication in the EU before the application for marketing authorization is made. Orphan drugs in Europe enjoy economic and marketing benefits, including up to ten years of market exclusivity for the approved indication unless another applicant can show that its product is safer, more effective or otherwise clinically superior to the orphan-designated product.

Reimbursement

Significant uncertainty exists regarding the coverage and reimbursement status of products approved by the FDA and other government authorities. In the United States, sales of any products for which we may receive regulatory approval for commercial sale will depend in significant part on the availability and adequacy of coverage and reimbursement from third-party payors. Third-party payors include government authorities, managed care providers, private health insurers and other organizations. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the reimbursement rate that the payor will pay for the product. Third-party payors may limit coverage to specific products on an approved list which might not include all of the FDA-approved products for a particular indication. Moreover, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

Third-party payors are increasingly challenging the prices charged for, examining the medical necessity of, and assessing the cost-effectiveness of medical products and services, in addition to their safety and efficacy. In order to obtain coverage and reimbursement for any product that might be approved for sale, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of any products, in addition to the costs required to obtain regulatory approvals. Our drug candidates may not be considered medically necessary or cost-effective. If third-party payors do not consider a product to be cost-effective compared to other available therapies, they may not cover the product after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its products at a profit.

The U.S. government and state legislatures have shown significant interest in implementing cost containment programs to limit the growth of government-paid health care costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. For example, the Patient Protection and Affordable Care Act, as amended the ACA, contains provisions that may reduce the profitability of drug products, including, for example, increased rebates for drugs reimbursed

by Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies' share of sales for branded prescription drugs to federal health care programs. Adoption of government controls and measures, and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for pharmaceuticals.

On August 16, 2022, President Biden signed into law the Inflation Reduction Act of 2022, or IRA, which, among other things, establishes Medicare Part B and Part D inflation rebate schemes. Failure to timely pay a Part B or Part D inflation rebate is subject to a civil monetary penalty. The IRA also creates a drug price negotiation program under which the prices for Medicare units of certain high Medicare spend drugs and biologics without generic or biosimilar competition will be capped by reference to, among other things, a specified non-federal average manufacturer price, starting in 2026. Failure to comply with requirements under the drug price negotiation program is subject to an excise tax and/or a civil monetary penalty. The IRA further makes changes to the Medicare Part D benefit, including a limit on annual out-of-pocket costs, and a change in manufacturer liability on account of a new discount program which could negatively affect the profitability of our product candidates. Failure to pay a discount under this new program will be subject to a civil monetary penalty. Congress continues to examine various policy proposals that may result in pressure on the prices of prescription drugs in the government health benefit programs. The IRA or other legislative changes could impact the market conditions for our product candidate. The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, an emphasis on cost containment measures in the United States has increased and we expect will continue to increase the pressure on pharmaceutical pricing. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

In addition, in some foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the EU provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products. Historically, products launched in the EU do not follow price structures of the United States and generally tend to be significantly lower

Human Capital

As of February 20, 2023, we had 92 full-time employees, including 66 engaged in research, development, and regulatory activities, and 26 in executive, commercial, general and administrative functions, and multiple part-time consultants. We believe that our future success will be shaped by our continued ability to attract and retain highly skilled employees. We provide our employees with competitive salaries and bonuses, opportunities for equity ownership in the Company, and an employment package that is designed to promote well-being across all aspects of their lives, including health care, disability, retirement investment options and paid time off.

General Information

We were incorporated in Delaware in September 2011. Our principal executive offices are located at 200 Barr Harbor Drive, Suite 200, West Conshohocken, PA 19428. Our Internet website address is www.madrigalpharma.com. No portion of our website is incorporated by reference into this Annual Report on Form 10-K.

We advise you to read this Annual Report on Form 10-K in conjunction with other reports and documents that we file from time to time with the SEC. In particular, please read our definitive proxy statement, which will be filed with the SEC in connection with our 2023 annual meeting of stockholders, our quarterly reports on Form 10-Q and any current reports on Form 8-K that we may file from time to time. You may obtain copies of these reports after the date of this annual report directly from us or from the SEC at its website at www.sec.gov. We make our periodic and current reports available on our internet website, free of charge, as soon as reasonably practicable after such material is electronically filed with, or furnished to, the SEC.

Item 1A. Risk Factors

You should carefully consider the risks described below, together with all of the other information included in or incorporated by reference into this report, before making an investment decision. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties not presently known to us or that we do not currently believe are important to an investor may also harm our business. If any of the events, contingencies, circumstances or conditions described in the following risks actually occur, our business, financial condition or our results of operations could be seriously harmed. If that happens, the trading price of our common stock could decline and you may lose part or all of the value of any of our shares held by you.

Risks Relating 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 profitability is achieved, we may be unable 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 resmetirom and other future product candidates. As of December 31, 2022, we had an accumulated deficit of approximately $962.7 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 December 31, 2022, we had cash, cash equivalents and marketable securities of approximately $358.8 million. In the future, we intend to continue to conduct research and development, clinical testing, regulatory compliance and, if resmetirom 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 resmetirom or other future product candidates. We do not currently have the required approvals to market resmetirom 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 resmetirom, 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 resmetirom, or we experience significant delays in doing so, our business will be materially harmed.

The primary focus of our product development since mid- 2018 has been resmetirom, a liver-directed selective thyroid hormone receptor beta agonist for potential use in non-alcoholic steatohepatitis, or NASH. Successful continued development and ultimate regulatory approval of resmetirom for NASH 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 resmetirom. We will need to raise sufficient funds to successfully complete our clinical development program for resmetirom in NASH. The future regulatory and commercial success of resmetirom 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 resmetirom, including, but not limited to, our planned registrational clinical trials to obtain drug approval;
- the mechanism of action of resmetirom is complex and we do not know the degree to which it will translate into a therapeutic benefit, if any, in NASH 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 resmetirom is taken for prolonged periods such as in the treatment of NASH or any other indication;

- delay or inability to reach agreement with the FDA or comparable foreign regulatory authorities on acceptable clinical trial design;
- regulators, IRBs or ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may not be able to obtain adequate evidence from clinical trials of efficacy and safety for resmetirom in NASH or any other indication;
- we do not know the degree to which resmetirom will be accepted as a therapy by physicians, patients and payors, even if approved;
- in our clinical programs for resmetirom, 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 resmetirom, 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 clinical or regulatory agencies may require in a Phase 3 clinical trial of NASH or for approval of our product candidates; we also cannot be certain if we will be able to gain Subpart H approval of any of our product candidates based on surrogate endpoints;
- foreign clinical or regulatory agencies may require efficacy and safety endpoints for Phase 3 clinical trials that may not be favorable to us and different from the results we have observed to date in our current trials;
- other differences in the design of our ongoing and planned Phase 3 clinical trials of the treatment of NASH, including the use of a new tablet formulation of resmetirom and/or 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 Subpart H approval of resmetirom based on a surrogate endpoint, consistent with our ongoing Phase 3 trial, we will be required to conduct a post-approval clinical outcomes trial under conditions set by FDA 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 resmetirom for NASH;
- if approved for NASH, resmetirom 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 resmetirom; and
- we may not be able to obtain, maintain or enforce our patents and other intellectual property rights.

We could also encounter delays if a clinical trial is placed on clinical hold, suspended or terminated by us, the IRBs of the institutions in which such trials are being conducted, or the FDA, the competent authorities and/or ethics committees of the EU Member States or other regulatory authorities, if a clinical trial is recommended for suspension or termination by the Data Safety Monitoring Board, or DSMB, for such trial, or on account of changes to federal, state, or local laws. A suspension or termination may be imposed due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols,

inspection of the clinical trial operations or trial site by the FDA, EMA, competent authorities and/or ethics committees of the EU Member States or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a product or treatment, failure to establish or achieve clinically meaningful trial endpoints, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial.

Many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates. Further, the FDA, EMA or other regulatory authorities may disagree with our clinical trial design and our interpretation of data from clinical trials, or may change the requirements for approval even after they have reviewed and commented on the design for our clinical trials.

Our product development costs will increase if we experience delays in clinical testing or marketing approvals. We do not know whether any of our clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant clinical trial delays could also shorten any periods during which we may have the exclusive right to commercialize our product candidates and may allow our competitors to bring products to market before we do, potentially impairing our ability to successfully commercialize our product candidates and harming our business and results of operations. Any delays in our clinical development programs may harm our business, financial condition and results of operations significantly.

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 resmetirom, 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 resmetirom. If we or any of our future development partners are unable to develop, or obtain regulatory approval for, or, if approved, successfully commercialize resmetirom, 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 resmetirom, 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 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 results in any Phase 3 clinical trial in NASH. Furthermore, our ongoing and future trials will need to demonstrate sufficient safety and efficacy in large 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 resmetirom 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.

Resmetirom has neither received Subpart H or full regulatory approval for the treatment of NASH 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. Even if resmetirom receives Subpart H approval for the treatment of NASH or any other indication, we will be required to conduct post-approval confirmatory trials under conditions specified by FDA. Failure to complete the post-approval trial may jeopardize our ability to market resmetirom.

Further, 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 resmetirom 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 but are not limited to 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;
- challenges in identifying or recruiting sufficient study sites or investigators for 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 ongoing clinical trials will need to be restructured, will enroll an adequate number of patients on time, or will be completed on schedule, if at all, or whether future clinical trials will begin as planned or have similar future challenges. 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 foreign 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 resmetirom if we are unable to locate, enroll and maintain a sufficient number of eligible patients to participate. Our Phase 3 clinical trials have significantly more patients than were enrolled in our Phase 2 trials. Although we have satisfied Subpart H patient enrollment for MAESTRO-NASH, clinical enrollment is not complete as of December 31, 2022 and significant additional enrollment will be necessary and will be ongoing for some time. 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 MAESTRO-NASH Phase 3 trial, patients' willingness to undergo a liver biopsy involves risk factors. In addition, potential patients for resmetirom may not be adequately diagnosed or identified with the diseases which we are targeting or may not meet the entry criteria for our studies.

In addition, 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 resmetirom and statins in 39 normal healthy volunteers, which showed resmetirom 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 resmetirom 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 our clinical trials. We also may encounter difficulties in identifying and enrolling NASH patients with a stage of disease appropriate for our future clinical trials. We may not be able to initiate or continue clinical trials if we are unable to locate and maintain a sufficient number of eligible patients to participate in the clinical trials required (or as may be required) by the FDA or other foreign regulatory agencies. In addition, the process of finding and diagnosing patients is costly and may prove more costly in the future. Our inability to enroll a sufficient number of patients for any of our clinical trials could 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.

We have received Fast Track Designation from the FDA for resmetirom for NASH; however, such designation may not actually lead to a faster development or regulatory review or approval process, and the designation may be rescinded if the product candidate no longer meets the qualifying criteria for Fast Track.

In October 2019, FDA granted Fast Track designation to resmetirom for NASH. Products that have been designated as Fast Track may be eligible for certain action to expedite development and review of the application, including rolling review. The receipt of Fast Track designation for a product candidate may not result in a faster development process, review or approval compared to products considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, the FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program.

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. As such, we and our contract manufacturers will be subject to periodic review and inspections to assess compliance with cGMP and adherence to commitments made in any NDA or other marketing application and previous responses to inspection observations. Accordingly, we and others with whom we work must continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production and quality control. In addition, any regulatory approvals that we receive for resmetirom may also be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, and will contain requirements for 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 marketing or manufacturing of our products, withdrawal of the product from the market;
- holds on clinical trials;
- 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 we may, 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 resmetirom.

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 our 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 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, as amended, (the ACA) became law in the United States. The goal of the ACA is to reduce the cost of healthcare and substantially change the way healthcare is financed by both government and private insurers. 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. Additional legislative changes to and regulatory changes under the ACA remain possible, but the nature and extent of such potential additional changes are uncertain at this time. We expect that the ACA, its implementation, efforts to challenge or modify the ACA or its implementing regulations, or portions thereof, and other healthcare reform measures including those that may be adopted in the future, could have a material adverse effect on our industry generally and on our ability to maintain or increase sales of existing products or to successfully commercialize product candidates, if approved.

On August 16, 2022, President Biden signed into law the IRA, which, among other things, establishes Medicare Part B and Part D inflation rebate schemes. Failure to timely pay a Part B or Part D inflation rebate is subject to a civil monetary penalty. The IRA also creates a drug price negotiation program under which the prices for Medicare units of certain high Medicare spend drugs and biologics without generic or biosimilar competition will be capped by reference to, among other things, a specified non-federal average manufacturer price, starting in 2026. Failure to comply with requirements under the drug price negotiation program is subject to an excise tax and/or a civil monetary penalty. The IRA further makes changes to the Medicare Part D benefit, including a limit on annual out-of-pocket costs, and a change in manufacturer liability under a new discount program which could negatively affect the profitability of our product candidates. Failure to pay a discount under this new program will be subject to a civil monetary penalty. Congress continues to examine various policy proposals that may result in pressure on the prices of prescription drugs in the government health benefit programs. The IRA or other legislative changes could impact the market conditions for our product candidate.

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 resmetirom 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 President, Research and Development, and 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 do not have significant marketing, sales or distribution infrastructure with respect to our product candidates. If we are unable to fully 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 do not have significant marketing, sales or distribution capabilities and have limited sales or marketing experience within our organization. If our lead product candidate, resmetirom, is approved, we intend to establish a sales and marketing organization with technical expertise and supporting distribution capabilities to commercialize resmetirom in the United States, and to license or outsource this function to a third party or third parties outside of the United States. 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 resmetirom. 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 resmetirom 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 resmetirom or any other future product candidate, we 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 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 Act 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 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 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 or fraudulent claim for payment of government funds, or knowingly making, using, or causing to be made or used, a false record or statement material to a false or fraudulent claim to the federal government, or knowingly concealing or knowing and improperly avoiding, decreasing, or concealing an obligation to pay money to the federal government. 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. There are other federal and state anti-fraud and abuse laws and regulations, as well as laws that require reporting of payments to certain health care professionals and adoption of certain compliance program requirements, that will govern our operations if and when we begin commercializing our products.

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, and its implementing regulations (“HIPAA”), which impose specified requirements relating to the privacy, security and transmission of protected 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 sued or found to have violated these laws for a variety of promotional and marketing and other activities, such as: providing free trips, free goods, sham consulting fees and grants and other monetary benefits to prescribers; reporting to pricing services average prices that are then used by federal programs to set reimbursement rates, rebates, and discounts; engaging in off-label promotion; and knowingly submitting false pricing information to the federal government, knowingly misrepresenting that information, or failing to timely submit that information. Pharmaceutical companies may further be found liable for civil monetary penalties for knowing and intentionally overcharging covered entities under the 340B Drug Pricing Program.

Additionally, in order to be eligible to have its products paid for with federal funds under the Medicaid and Medicare Part B programs and purchased by the Department of Veterans Affairs ("VA"), Department of Defense ("DoD"), Public Health Service, and Coast Guard (the "Big Four agencies") and certain federal grantees, a manufacturer is required to list its innovator products on a VA Federal Supply Schedule ("FSS") contract and charge a price to the Big Four agencies that is no higher than the Federal Ceiling Price ("FCP"), which is a price calculated pursuant to a statutory formula. In addition, manufactures must submit to the VA quarterly and annual "non federal average manufacturer price" ("Non FAMP") calculations for each NDC-11 of their innovator drugs. Under Section 703 of the National Defense Authorization Act for FY 2008, the manufacturer is required to pay quarterly rebates to DoD on utilization of its innovator products that are dispensed through DoD's Tricare network pharmacies to Tricare beneficiaries. 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 our operations are found to be in violation of any of the federal and state laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including (depending on the applicable law) criminal and significant civil monetary penalties, damages, fines, imprisonment, exclusion from participation in government programs, injunctions, recall or seizure of products, total or partial suspension of production, denial or withdrawal of pre-marketing product approvals, private ''qui tam'' actions brought by individual whistleblowers in the name of the government or refusal to allow us to enter into supply contracts, including government contracts, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

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 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 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. For example, 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.

Our internal computer systems, or those of our third-party collaborators, service providers, contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our development programs and have a material adverse effect on our reputation, business, financial condition or results of operations.

Our internal computer systems and those of our current or future third-party collaborators, service providers, contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. Attacks on information technology systems are increasing in their frequency, levels of persistence, sophistication and intensity, and they are being conducted by increasingly sophisticated and organized groups and individuals with a wide range of motives and expertise. In addition to extracting sensitive information, such attacks could include the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information. The prevalent use of mobile devices also increases the risk of data security incidents. While we have not experienced any material system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations or the operations of third-party collaborators, service providers, contractors and consultants, it could result in a material disruption of our development programs and significant reputational, financial, legal, regulatory, business or

operational harm. For example, the loss of clinical trial data for our product candidates could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our data or applications or other data or applications relating to our technology or product candidates, or inappropriate disclosure of confidential or proprietary information, we could incur liabilities and the further development of our product candidates could be delayed. In addition, our liability insurance may not be sufficient in type or amount to cover us against claims related to security breaches, cyberattacks and other related breaches.

Any failure or perceived failure by us or any third-party collaborators, service providers, contractors or consultants to comply with our privacy, confidentiality, data security or similar obligations to third parties, or any data security incidents or other security breaches that result in the unauthorized access, release or transfer of sensitive information, including personally identifiable information, may result in governmental investigations, enforcement actions, regulatory fines, litigation or public statements against us, could cause third parties to lose trust in us or could result in claims by third parties asserting that we have breached our privacy, confidentiality, data security or similar obligations, any of which could have a material adverse effect on our reputation, business, financial condition or results of operations. Moreover, data security incidents and other security breaches can be difficult to detect, and any delay in identifying them may lead to increased harm. While we have implemented data security measures intended to protect our information technology systems and infrastructure, there can be no assurance that such measures will successfully prevent service interruptions or data security incidents that could adversely affect our business.

Failure to comply with health and data protection laws and regulations could lead to government enforcement actions (which could include civil or criminal penalties), private litigation and/or adverse publicity, and could negatively affect our operating results and business.

We may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA imposes privacy and security obligations on covered entity health care providers, health plans, and health care clearinghouses, as well as their "business associates" – certain persons or covered entities that create, receive, maintain, or transmit protected health information in connection with providing a specified service or performing a function on behalf of a covered entity. We could potentially be subject to criminal penalties if we, our affiliates, or our agents knowingly receive individually identifiable health information maintained by a HIPAA-covered entity in a manner that is not authorized or permitted by HIPAA.

To the extent we collect California resident personal information, we may also be subject to the CCPA. The CCPA, created new transparency requirements and granted California residents several new rights with regard to their personal information. In addition, California voters approved the California Privacy Rights Act ("CPRA") ballot initiative which introduced significant amendments to the CCPA and established and funded a dedicated California privacy regulator, the California Privacy Protection Agency ("CPPA"). The amendments introduced by the CPRA went into effect on January 1, 2023, and new implementing regulations are expected to be introduced by the CPPA. Failure to comply with the CCPA may result in, among other things, significant civil penalties and injunctive relief, or statutory or actual damages. In addition, California residents have the right to bring a private right of action in connection with certain types of incidents. These claims may result in significant liability and damages. Virginia and Colorado also adopted laws, effective January 1, 2023, and July 1, 2023, respectively, introducing new privacy obligations for which we may need to take additional steps to comply. Similarly, there are a number of legislative proposals in the United States, at both the federal and state level, that could impose new obligations or limitations in the area of consumer protection. For example, Utah and Connecticut have enacted privacy laws similar to the CCPA that impose new obligations or limitations in areas affecting our business. These laws and regulations are evolving and may impose limitations on our business activities. The obligations to comply with new privacy laws may require us, among other things, to update our notices and develop new processes internally and with our third-party collaborators, service providers, contractors or consultants to facilitate consumer rights requests, and such laws may impose restrictions on our processing of personal information that may impact the way we operate our business. We may be subject to fines,

penalties, or private actions in the event of non-compliance with such laws. The CCPA, the CPRA or other domestic privacy and data protection laws and regulations may increase our compliance costs and potential liability.

European data collection is governed by restrictive regulations governing the use, processing and cross-border transfer of personal information.

Outside the United States, our clinical trial programs and operations implicate international data protection laws, including the EU General Data Protection Regulation 2016/679 ("GDPR"). The GDPR increases our responsibility and liability in relation to the processing of personal data of individuals located in the EU. The GDPR, together with the national legislation of the EU member states governing the processing of personal data, impose strict obligations and restrictions on the ability to collect, analyze and transfer personal data, including health data and samples from clinical trials and adverse event reporting. In particular, these obligations and restrictions concern the consent of the individuals to whom the personal data relates, the processing details disclosed to the individuals, the sharing of personal data with third parties, the transfer of personal data out of the EU, security breach notifications, as well as substantial potential fines for violations of the data protection obligations. Specifically regarding the transfer of personal data outside of the EU, while there are legal mechanisms available to lawfully transfer personal data outside of the EU, including to the United States, there are certain unsettled legal issues regarding such data transfers, the resolution of which may adversely affect our ability to transfer personal data or otherwise may cause us to incur significant costs to come into compliance with applicable data transfer impact assessments and implementation of legal data transfer mechanisms. On July 16, 2020, the European Court of Justice ruled the EU-US Privacy Shield to be an invalid data transfer mechanism and confirmed that the Model Clauses remain valid, and in June 2021, the European Commission published updated versions of the Model Clauses, which must be incorporated into new and existing agreements within prescribed timeframes in order to continue to lawfully transfer personal data outside of the EU. Data protection authorities from the different EU member states, as well as in the United Kingdom and Switzerland, have promulgated national privacy laws that impose additional requirements, which add to the complexity of processing and transferring EU personal data, with the United Kingdom and Switzerland following the EU with the publication of new Model Clauses to be incorporated in all applicable contracts within a specified timeframe in order to legitimize data transfers from those jurisdictions. The UK adopted versions of their Model Clauses during 2022. Our ability to continue to transfer personal data outside of the EU, United Kingdom, or Switzerland may become significantly more expensive and may subject us to increased scrutiny and liability under the GDPR or similar local laws, and we may experience operating disruptions if we are unable to conduct these transfers in the future.

On December, 13 2022, the European Commission adopted a draft adequacy decision for the EU-U.S. Data Privacy Framework, which reflects the assessment by the European Commission of the US legal framework. The draft decision concludes that the United States ensures an adequate level of protection for personal data transferred from the EU to U.S. companies. After an approval process, the European Commission is expected to adopt the final adequacy decision, which will allow data to flow freely from the EU to the U.S.

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 resmetirom granted to us by Roche.

We entered into a Research, Development and Commercialization Agreement, or the Roche Agreement, with Hoffmann-La Roche, or Roche, on December 18, 2008. Pursuant to the terms of the Roche Agreement, we assumed control of all development and commercialization of resmetirom and hold exclusive worldwide rights for all potential indications. Under the Roche Agreement, Roche exclusively licensed certain patent rights and know-how relating to resmetirom 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 resmetirom or another licensed product, subject to certain reductions. 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 resmetirom, or (ii) ten years after the first sale of a product containing resmetirom. 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 resmetirom, 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 resmetirom and may lead to a complete termination of the Roche Agreement and force us to cease product development efforts for resmetirom.

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. While we have licensed rights to issued patents in the United

States and other jurisdictions for resmetirom, we cannot be certain that the claims in issued 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 may 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 composition-of-matter patent licensed from Roche relating to resmetirom is scheduled 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 resmetirom to treat various indications are scheduled to expire in 2033. Our exclusively-owned pending patent applications that cover companion diagnostics, various solid forms of resmetirom, combination therapy, method of use, and method of manufacturing, if issued, are expected to expire between 2037 and 2042. Our exclusively-owned pending patent application that covers other THR beta analogs and uses thereof, if issued, is expected to expire in 2043. 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 our 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 resmetirom 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 resmetirom for NASH 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 resmetirom 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 resmetirom 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 resmetirom 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 patents directed at resmetirom in the United States and other countries, filing, prosecuting and defending patents on resmetirom 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 resmetirom, 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 Relating to Our Financial Position and Need for Capital

If we fail to obtain the capital necessary to fund all of our planned operations, we may be unable to successfully develop and commercialize resmetirom 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 will require additional working capital in order to complete the remaining clinical development primarily for resmetirom and potentially for other product candidates through potential regulatory approval and through potential commercialization of these product candidates. We expect our spending levels overall to increase in connection with our clinical trials of resmetirom 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 future clinical trials and projected product label or the need for additional clinical trials of resmetirom for NASH and dyslipidemia 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 resmetirom for NASH and any of our other potential product candidates;
- the costs and timing of obtaining or maintaining manufacturing for resmetirom for NASH 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, including for ex-US resmetirom opportunities;
- costs associated with any new product candidates that we may develop, in-license or acquire; and
- the effect of competing technological and market developments.

Some of these factors are outside of our control. Our existing capital resources may not be sufficient to enable us to fund the completion of all planned clinical trials and commercialization objectives for our product

candidates. These and other circumstances may cause us to delay certain research activities and related clinical expenses, but such delays will not alter our need to raise additional funding. As a result, 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 or have a potential restrictive effect on how we operate our business. In addition, market perception that we need to issue additional shares, 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 need to delay certain aspects of, or be unable to complete, planned clinical trials for resmetirom for NASH and 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 our Indebtedness

Our Loan and Security Agreement contains restrictive and financial covenants that may limit our operating flexibility.

On May 6, 2022, we and our subsidiary, Canticle Pharmaceuticals, Inc. ("Canticle") entered into a Loan and Security Agreement with Hercules, as amended on February 3, 2023 (as amended, the "Loan Agreement"), providing for an aggregate of $250.0 million in term loans that will be available to us in four tranches subject to the conditions set forth in the Loan Agreement (collectively, the "Term Loans"). Our obligations under the Loan Agreement are secured by a security interest in substantially all of our assets, other than intellectual property. Until we have repaid such indebtedness, the Loan Agreement subjects us to various terms, conditions and covenants. These include financial reporting obligations, and certain limitations on indebtedness, liens (including a negative pledge on intellectual property and other assets), investments, distributions (including dividends), collateral, investments, distributions, transfers, mergers or acquisitions, taxes, corporate changes, and deposit accounts. Additionally, the Loan Agreement contains affirmative and restrictive financial covenants commencing on January 1, 2023, including maintenance of a minimum cash, cash equivalents and liquid funds covenant of $35.0 million, which may decrease in certain circumstances if the Company achieves both a certain FDA approval for resmetirom and a revenue milestone (the "Minimum Cash Covenant"). The Loan Agreement also includes a revenue-based covenant (the "Revenue Covenant") that could apply commencing at or after the

time that financial reporting is due for the quarter ending September 30, 2024; however, the Revenue Covenant will be waived at any time in which the Company maintains, as measured monthly (i) a certain level of cash, cash equivalents and liquid funds relative to outstanding Hercules debt or (ii) a market capitalization of at least $1.2 billion. The Revenue Covenant, as and when effective on or after November of 2024, would require the Company to maintain a minimum amount of trailing three-month net product revenue. Our business may be adversely affected by these restrictions on our ability to operate our business. If we raise any additional debt financing, as permitted by the Loan Agreement and if pursued and secured by the Company, the terms of such additional debt could further restrict our operating and financial flexibility.

We may not be able to generate sufficient cash flow or sales to meet the financial covenants or pay the principal and interest under the Term Loans. Furthermore, our future working capital, borrowings or equity financing could be unavailable to repay or refinance the amounts outstanding under the Term Loans. In the event of a liquidation, the lender under the facility would be repaid all outstanding principal and interest prior to distribution of assets to unsecured creditors, and the holders of our common stock would receive a portion of any liquidation proceeds only if all of our creditors then existing, including the lender under the Term Loans, were first repaid in full.

Our failure to comply with the covenants or other terms of the Loan Agreement, including as a result of events beyond our control, could result in a default under the Loan Agreement that could materially and adversely affect our business.

Additionally, we may be required to repay the outstanding indebtedness under the loan if an event of default occurs under the Loan Agreement or, if applicable, any future debt facility. The Loan Agreement includes customary events of default, including payment defaults, breaches of covenants following any applicable cure period, the occurrence of certain events that could reasonably be expected to have a "material adverse effect" as set forth in the Loan Agreement, and cross acceleration. We may not have enough available cash or be able to raise additional funds through equity or debt financings to repay such indebtedness at the time any such event of default occurs. In this case, we may be required to delay, limit, reduce or terminate our product development or commercialization efforts or grant to others rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves. Our business, financial condition and results of operations could be materially adversely affected as a result of any of these events.

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 closing price of our common stock has ranged from $55.89 to $296.54 per share during the period from January 1, 2022 to January 31, 2023. The market price of our common stock could be impacted due to a variety of factors, including: global market or financial developments; prevailing macroeconomic conditions, including potential recession or economic downturns; US market events (including the potential for unusual market trading activity following external short interest developments or social media activity); the outbreak of war or hostilities; NASH therapeutic company developments and/or FDA developments, regardless of whether occurring generally and/or specifically as to our clinical trials and development programs; industry-wide events; and the following events or developments:

- the losses we may incur, including increased losses resulting from costs associated with increases in our clinical trial activity;
- developments in patent or other proprietary rights owned or licensed by us, our collaborative partners or our competitors;
- the progress and results of our clinical trials;

- public or regulatory concern as to the safety and efficacy of NASH products developed by us or others or public safety generally; 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 the event any of the foregoing occur, the market price of our common stock could be highly volatile and may materially decline.

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

Certain stockholders affiliated and associated with our officers and directors collectively own approximately 21.9% of our outstanding common stock as of December 31, 2022 and acting together, may have the ability to substantially 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. 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. We have in the past utilized an “at-the-market” (“ATM”) sales program to raise capital by selling our securities through a sales agent up to established limits, and have also issued shares of our common stock in registered offerings and shares of convertible preferred equity to institutional investors in registered and private direct offerings. We expect that significant additional capital will be needed in the future to continue our planned operations. To the extent we raise additional capital or convertible securities, through any ATM program, public equity offering, direct offering, private offering or otherwise, our stockholders may experience substantial dilution. 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 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 December 31, 2022, there were a number of investors or investor groups that held a significant beneficial ownership interest in our common stock, including: 2,049,629 shares of our outstanding common stock

(the "Bay City Affiliate Holdings") beneficially owned by Dr. Fred Craves, our Lead Director, which includes 1,511,782 shares beneficially owned by Bay City Capital LLC ("Bay City"); 2,119,603 shares of our outstanding common stock beneficially owned by Drs. Paul Friedman and Becky Taub (the "Friedman/Taub Holdings"), our Chairman and Chief Executive Officer and President of R&D and Chief Medical Officer, respectively; 1,969,797 shares of outstanding Series A Convertible Preferred stock and 400,000 shares of outstanding Series B Convertible Preferred Stock (collectively, the "Common Shares Underlying Our Preferred Stock"), each of which are common stock equivalents with no voting rights, that are convertible into shares of Common Stock on a 1-for-1 basis only to the extent that after giving effect to such conversion the holders thereof and their affiliates and any persons who are members of a Section 13(d) group with the holders or their affiliates would beneficially own (in the aggregate, for purposes of Rule 13d-3 under the Exchange Act) no more than 4.99% of the outstanding Common Stock, subject to adjustment with 61 days' notice and certain limitations (the "Beneficial Ownership Limitation"); and 2,857,054 shares of our common stock issuable upon the exercise of outstanding stock options under our 2015 Stock Plan, as amended and 14,899 shares of our common stock issuable upon the exercise of outstanding vested warrants held by our creditors (the "Common Shares Underlying Our Stock Options and Warrants"). In addition, there are other institutional investors who from time to time file Schedule 13Gs (or amendments thereto) or Form 13Fs reflecting substantial beneficial ownership of outstanding common stock ("Our Other Shares Beneficially Owned by Institutional Investors").

The Bay City Affiliate Holdings and the Friedman/Taub Holdings collectively represent beneficial ownership of approximately 21.9% of our outstanding common stock as of December 31, 2022, and are capable of being sold directly (including by Bay City or its affiliated funds) or indirectly (following any future distribution to Bay City from affiliated funds, to Bay City fund limited partners, or by Bay City to its partners), and any material sale of such shares could significantly reduce the market price of our common stock and impair our ability to raise adequate capital. As of December 31, 2022, the 2,369,797 Common Shares Underlying Our Preferred Stock (disregarding the Beneficial Ownership Limitation and assuming the full conversion of all currently outstanding preferred shares) owned by entities affiliated with Baker Bros. Advisors LP and 1,545,113 additional shares of common stock directly owned by entities affiliated with Baker Bros. Advisors LP collectively represented beneficial ownership of approximately 19.1% of our common stock on an as converted basis (the "Baker Bros. Fully Converted Interest").

Sales of a substantial number of shares of our common stock by one or more of the investors or groups listed above (such as the Common Shares Underlying Our Preferred Stock, the Bay City Affiliate Holdings, the Friedman/Taub Holdings, the Baker Bros. Fully Converted Interest, the Common Shares Underlying Our Stock Options and Warrants and Our Other Shares Beneficially Owned by Institutional Investors) 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. See "Risk Factors; Risks Relating to Ownership of Our Common Stock — The price of our common stock has been, and may continue to be, volatile." Such sales or short 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.

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.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

As of December 31, 2022, we leased our approximately 30,500 square-foot corporate headquarters facility located in West Conshohocken, Pennsylvania. We believe our facility is adequate for our current needs. Our lease contains extension rights beyond the scheduled lease expiration date of November 30, 2023. We plan to lease or acquire additional space as our business continues to grow. We continue to evaluate our facility requirements and believe that appropriate space will be available to accommodate our future needs.

Item 3. Legal Proceedings

We currently are not a party to any material legal proceedings.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

Market Information

Our common stock has traded on the Nasdaq stock market under the symbol "MDGL" since July 25, 2016. Prior to July 25, 2016, our common stock was traded on the Nasdaq stock market under the symbol "SNTA."

Holders

As of December 31, 2022, there were approximately 43 holders of record of our common stock. This number does not include "street name" or beneficial holders, whose shares are held of record by banks, brokers, financial institutions and other nominees. In addition, we had two holders of record who owned shares of our Series A Convertible Preferred Stock and Series B Convertible Preferred Stock.

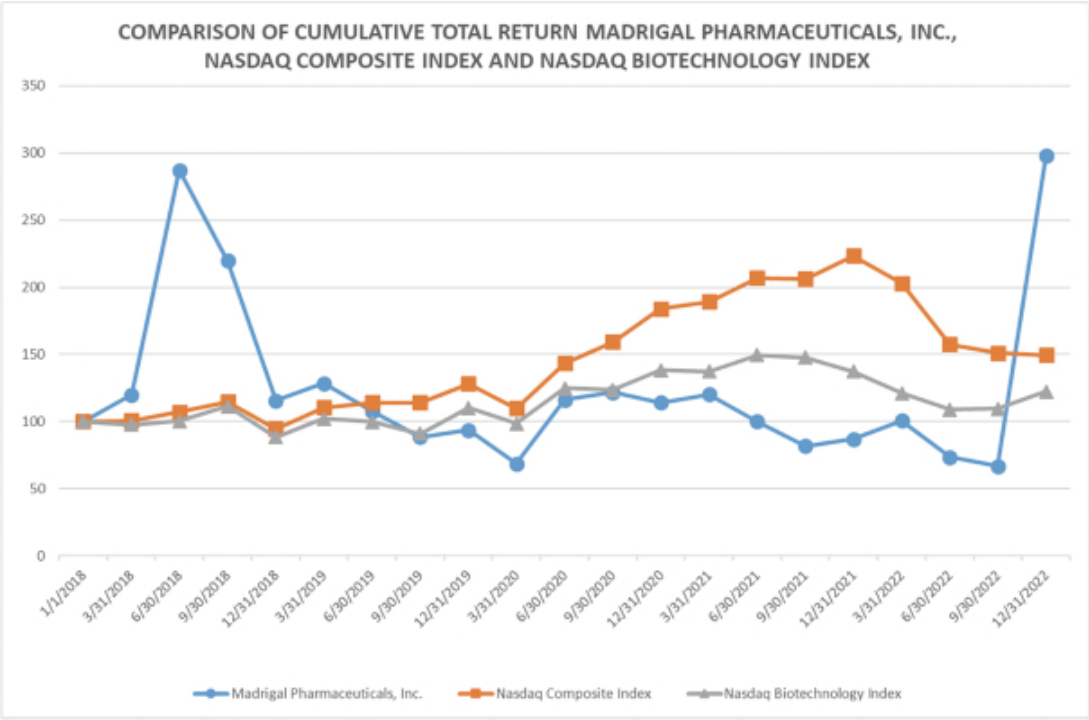
Dividends

We have not paid any cash dividends on our common stock. We currently intend to retain all available funds and any future earnings to fund the development and expansion of our business, and we do not anticipate paying any cash dividends in the foreseeable future. Any future determination to pay cash dividends will be at the discretion of our board of directors and will depend on our financial condition, results of operations, contractual restrictions, capital requirements, and other factors that our board of directors deems relevant.

Stock Performance Graph

The graph set forth below compares the cumulative total stockholder return on our common stock between January 1, 2018 and December 31, 2022, with the cumulative total return of (a) the Nasdaq Biotechnology Index and (b) the Nasdaq Composite Index, over the same period. This graph assumes the investment of $100 on January 1, 2018 in our common stock, the Nasdaq Biotechnology Index and the Nasdaq Composite Index and assumes the reinvestment of dividends, if any.

The comparisons shown in the graph below are based upon historical data. We caution that the stock price performance shown in the graph below is not necessarily indicative of, nor is it intended to forecast, the potential future performance of our common stock.



The above Stock Performance Graph and related information shall not be deemed to be "soliciting material" or to be "filed" with the Securities and Exchange Commission, nor shall such information be incorporated by reference into any future filing under the Securities Act of 1933 or Securities Exchange Act of 1934, each as amended, except to the extent that we specifically request that such information be treated as soliciting material or specifically incorporate it by reference into a filing.

Item 6. [Reserved]

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

The Risk Factors in Part I, Item 1A and disclosures under "Cautionary Note Regarding Forward-Looking Statements" within this Annual Report on Form 10-K, the audited financial statements and accompanying notes, included elsewhere in this Annual Report on Form 10-K, and this Management's Discussion and Analysis of Financial Condition and Results of Operations should be read together. In addition to historical information, this discussion and analysis contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Exchange Act of 1934, as amended, or the Exchange Act, that involve risks and uncertainties, such as statements of our plans, objectives, expectations and intentions. As disclosed in this report, our actual results could differ materially from those discussed in these forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in "Cautionary Note Regarding Forward-Looking Statements" and in the "Risk Factors" sections contained in Part I, Item 1A in this Annual Report on Form 10-K. Our operating results are not necessarily indicative of results that may occur for the full fiscal year or any other future period.

About Madrigal Pharmaceuticals, Inc.

Our Focus. We are a clinical-stage biopharmaceutical company pursuing novel therapeutics for nonalcoholic steatohepatitis, or NASH. Our lead product candidate, resmetirom, is a proprietary, liver-directed, selective thyroid hormone receptor-ß, or THR-ß, agonist being developed as a once-daily oral pill for the treatment of NASH.

Our Patient Market Opportunity. 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. NASH can progress to cirrhosis or liver failure, require liver transplantation and can also result in liver cancer. Progression of NASH to end stage liver disease will soon surpass all other causes of liver failure requiring liver transplantation. Importantly, beyond these critical conditions, NASH and NAFLD patients additionally suffer heightened cardiovascular risk and, in fact, die more frequently from cardiovascular events than from liver disease. NASH and NAFLD have grown as a consequence of rising worldwide obesity-related disorders. In the United States, NAFLD is estimated to affect approximately 25% of the population, and approximately 25% of those will progress from NAFLD to NASH. Current estimates place NASH prevalence at approximately 22 million people in the United States by 2024, 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.

Our Completed Studies. For NASH, we enrolled 125 patients in a Phase 2 clinical trial with resmetirom. 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 also completed a 36-week, open-label extension study in 31 participating NASH patients from our Phase 2 clinical trial, which included 14 patients who received placebo in the main study.

On December 18, 2019 the Company announced it had opened for enrollment MAESTRO-NAFLD-1, a 52-week, non-invasive, multi-center, double-blind, placebo-controlled Phase 3 clinical study of patients with biopsy-confirmed or presumed NASH recruited from sites in the U.S. Key endpoints are safety, including safety biomarkers. Secondary endpoints include LDL cholesterol, lipid biomarkers, MRI-PDFF, NASH and fibrosis biomarkers. Except for serial liver biopsies, the study protocol is similar to the MAESTRO-NASH study (discussed below under "—Our Ongoing and Planned Studies"), with resmetirom doses of 80 mg or 100 mg or placebo. Enrollment objectives for this study were exceeded, with approximately 1,300 patients enrolled overall. The MAESTRO-NAFLD-1 study will help support the adequacy of the safety database at the time of NDA submission for Subpart H approval for treatment of patients with NASH with fibrosis. In November of 2021, we

reported data from the open label non-cirrhotic arm of MAESTRO-NAFLD-1, and in January 2022 we announced that we achieved primary and secondary endpoints for the double-blind portion of MAESTRO-NAFLD-1, as summarized in "- Key Developments" below.

Our Ongoing and Planned Studies. On March 28, 2019, the Company announced that it had initiated MAESTRO-NASH, a Phase 3 trial in NASH with its once daily, oral thyroid hormone receptor beta selective agonist, resmetirom. This double-blind, placebo-controlled study is being conducted at more than 220 sites in the United States and the rest of the world. MAESTRO-NASH is a multicenter, randomized, double-blind, placebo-controlled Phase 3 study of resmetirom in patients with liver biopsy-confirmed NASH and was initiated in March 2019. The subpart H portion of the study enrolled more than 1,000 patients with biopsy-proven NASH (at least half with F3 (advanced) fibrosis, the remainder F2 or F1B (moderate fibrosis) with a few earlier F1 patients), randomized 1:1:1 to receive once-daily resmetirom 80 mg, resmetirom 100 mg, or placebo. After 52 weeks of treatment, a second liver biopsy is performed. The dual primary surrogate endpoints on biopsy are NASH resolution with ≥2-point reduction in NAS (NAFLD Activity Score), and with no worsening of fibrosis OR a 1-point decrease in fibrosis with no worsening of NAS. Achievement of either primary endpoint is considered a successful trial outcome. A key secondary endpoint is lowering of LDL-C. All patients enrolled in the MAESTRO-NASH study (up to 2,000 in total) continue on therapy after the initial 52-week treatment period for up to 54 months to accrue and measure hepatic clinical outcome events including progression to cirrhosis on biopsy (52 weeks and 54 months) and hepatic decompensation events, as well as all-cause mortality. In December 2022, we reported topline results from the subpart H portion of the study: resmetirom achieved both primary endpoints with both daily oral doses, 80 mg and 100 mg, relative to placebo, as summarized in "- Key Developments" below.

On July 13, 2021 we announced first patient dosed in a planned 52-week open label active treatment extension study of MAESTRO-NAFLD-1, named MAESTRO-NAFLD-Open Label Extension (OLE). The OLE study allows patients who complete MAESTRO-NAFLD-1 to consent to 52 weeks of active treatment with resmetirom, making this treatment available to both patients who were assigned to placebo in MAESTRO-NAFLD-1 and patients who were on resmetirom in MAESTRO-NAFLD-1.

In August 2022, Madrigal initiated MAESTRO-NASH-OUTCOMES, a randomized double-blind placebo-controlled study in approximately 700 patients with early NASH cirrhosis to allow for noninvasive monitoring of progression to liver decompensation events. A positive outcome is expected to support the full approval of resmetirom for noncirrhotic NASH, potentially accelerating the timeline to full approval. In addition, this study has the potential to support an additional indication for resmetirom in patients with well-compensated NASH cirrhosis.

Key Developments

In December 2022, Madrigal announced topline results from the pivotal Phase 3 MAESTRO-NASH biopsy study of resmetirom. Madrigal reported that resmetirom achieved both primary endpoints with both daily oral doses, 80 mg and 100 mg, relative to placebo. For additional details on these topline results and other recent developments, see: "Business: Key Developments."

Basis of Presentation

Research and Development Expenses

Research and development expenses primarily consist of costs associated with our research activities, including the preclinical and clinical development of our product candidates. We expense our research and development expenses as incurred. We contract with clinical research organizations to manage our clinical trials under agreed upon budgets for each study, with oversight by our clinical program managers. We account for nonrefundable advance payments for goods and services that will be used in future research and development

activities as expenses when the service has been performed or when the goods have been received. Manufacturing expense includes costs associated with drug formulation development and clinical drug production. We do not track employee and facility related research and development costs by project, as we typically use our employee and infrastructure resources across multiple research and development programs. We believe that the allocation of such costs would be arbitrary and not be meaningful.

Our research and development expenses consist primarily of:

- salaries and related expense, including stock-based compensation;
- external expenses paid to clinical trial sites, contract research organizations, laboratories, database software and consultants that conduct clinical trials;
- expenses related to development and the production of nonclinical and clinical trial supplies, including fees paid to contract manufacturers;
- expenses related to preclinical studies;
- expenses related to compliance with drug development regulatory requirements; and
- other allocated expenses, which include direct and allocated expenses for depreciation of equipment and other supplies.

We expect to continue to incur substantial expenses related to our development activities for the foreseeable future as we conduct our clinical studies programs, manufacturing and toxicology studies. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials, additional drug manufacturing requirements, and later stage toxicology studies such as carcinogenicity studies. Our research and development expenses have increased year over year in each of 2020, 2021, and 2022 and we expect that our research and development expenses will increase substantially in the future. The process of conducting preclinical studies and clinical trials necessary to obtain regulatory approval is costly and time consuming. The probability of success for each product candidate is affected by numerous factors, including preclinical data, clinical data, competition, manufacturing capability and commercial viability. Accordingly, we may never succeed in achieving marketing approval for any of our product candidates.

Completion dates and costs for our clinical development programs as well as our research program can vary significantly for each current and future product candidate and are difficult to predict. As a result, we cannot estimate with any degree of certainty the costs we will incur in connection with the development of our product candidates at this point in time. We expect that we will make determinations as to which programs and product candidates to pursue and how much funding to direct to each program and product candidate on an ongoing basis in response to the scientific success of early research programs, results of ongoing and future clinical trials, our ability to enter into collaborative agreements with respect to programs or potential product candidates, as well as ongoing assessments as to each current or future product candidate's commercial potential.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries, benefits and stock-based compensation expenses for employees, management costs, costs associated with obtaining and maintaining our patent portfolio, professional fees for accounting, auditing, consulting and legal services, and allocated overhead expenses.

We expect that our general and administrative expenses will increase in the future as we expand our operating activities, maintain and expand our patent portfolio and incur additional costs associated with being a public company and maintaining compliance with exchange listing and SEC requirements. We expect these potential increases will likely include management costs, legal fees, accounting fees, directors' and officers' liability insurance premiums and expenses associated with investor relations.

Critical Accounting Policies and Estimates

Our management's discussion and analysis of our financial condition and results of operations are based on our financial statements which have been prepared in accordance with GAAP. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets and liabilities, and expenses and the disclosure of contingent assets and liabilities at the date of the financial statements. On an ongoing basis, we evaluate our estimates and judgments, including those related to accrued research and development expenses. We base our estimates on historical experience, known trends and events, and various other factors that are believed to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ materially from these estimates under different assumptions or conditions.

Research and Development Costs

Research and development costs are expensed as incurred. Research and development costs are comprised of costs incurred in performing research and development activities, including internal costs (including stock-based compensation), costs for consultants, milestone payments under licensing agreements, and other costs associated with the Company's preclinical and clinical programs. In particular, the Company has conducted safety studies in animals, optimized and implemented the manufacturing of our drug, and conducted Phase 1-3 clinical trials, all of which are considered research and development expenditures. Management uses significant judgment in estimating the amount of research and development costs recognized in each reporting period. Management analyzes and estimates the progress of its preclinical studies and clinical trials, completion of milestones events per underlying agreements, invoices received and contracted costs when estimating the research and development costs to accrue in each reporting period. Actual results could differ from the Company's estimates. The Company's historical estimates for research and development costs have not been materially different from the actual costs.

Stock-Based Compensation

The Company recognizes stock-based compensation expense based on the grant date fair value of stock options granted to employees, officers and directors. The Company uses the Black-Scholes option pricing model to determine the grant date fair value as management believes it is the most appropriate valuation method for its option grants. The Black-Scholes model requires inputs for risk-free interest rate, dividend yield, volatility and expected lives of the options. The expected lives for options granted represent the period of time that options granted are expected to be outstanding. The Company uses the simplified method for determining the expected lives of options. Expected volatility is based upon an industry estimate or blended rate including the Company's historical trading activity. The risk-free rate for periods within the expected life of the option is based on the U.S. Treasury yield curve in effect at the time of the grant. The Company estimates the forfeiture rate based on historical data. This analysis is re-evaluated at least annually and the forfeiture rate is adjusted as necessary.

Certain of the employee stock options granted by the Company are structured to qualify as incentive stock options (ISOs). Under current tax regulations, the Company does not receive a tax deduction for the issuance, exercise or disposition of ISOs if the employee meets certain holding requirements. If the employee does not meet the holding requirements, a disqualifying disposition occurs, at which time the Company may receive a tax deduction. The Company does not record tax benefits related to ISOs unless and until a disqualifying disposition is reported. In the event of a disqualifying disposition, the entire tax benefit is recorded as a reduction of income tax expense. The Company has not recognized any income tax benefit for its share-based compensation arrangements due to the fact that the Company does not believe it is more likely than not it will realize the related deferred tax assets.

Results of Operations

Comparison of the Years Ended December 31, 2022 and 2021

Revenue

We did not generate any revenue during the years ended December 31, 2022 and 2021, respectively.

Operating Expenses

The following table provides comparative results of our operating expenses for the years ended December 31, 2022 and 2021 (in thousands):

	Year Ended December 31,		Increase / (Decrease)	
	2022	2021	$	%
Research and Development Expenses	$245,441	$205,164	40,277	20%
General and Administrative Expenses	48,130	37,318	10,812	29%
Interest (Income)	(2,185)	(363)	1,822	502%
Interest Expense	3,964	—	3,964	100%
Other (income)	—	(273)	(273)	(100%)
	$295,350	$241,846	53,504	22%

Research and Development Expense

Our research and development expenses were $245.4 million for the year ended December 31, 2022 compared to $205.2 million for the year ended December 31, 2021. Research and development expenses increased by $40.3 million in the 2022 period due primarily to the additional activities related to our Phase 3 clinical trials, an increase in headcount, and an increase in stock compensation expense. We expect our research and development expenses to increase as we advance our clinical and preclinical development programs for resmetirom.

General and Administrative Expense

Our general and administrative expenses were $48.1 million for the year ended December 31, 2022 compared to $37.3 million for the year ended December 31, 2021. General and administrative expenses increased by $10.8 million in the 2022 period due primarily to increases in commercial preparation activities, including corresponding increase in headcount, and an increase in stock compensation expense. We believe our general and administrative expenses may increase over time as we advance our clinical and preclinical development programs for resmetirom, prepare for commercialization, and expand our operating activities, which will likely result in an increase in our headcount, consulting services, and related overhead needed to support those efforts.

Interest Income

Our interest income was $2.2 million for the year ended December 31, 2022 compared to $0.4 million for the year ended December 31, 2021. The increase in interest income was due primarily to a higher average principal balance in our investment account in 2022 and increased interest rates.

Interest Expense

Our interest expense was $4.0 million for year ended December 31, 2022, compared to $0 million for the year ended December 31, 2021. The increase in interest expense was as a result of the Loan and Security Agreement (“Loan Facility”) we entered into with Hercules during the second quarter of 2022.

Comparison of the Years Ended December 31, 2021 and 2020

Revenue

We did not generate any revenue during the years ended December 31, 2021 and 2020, respectively.

Operating Expenses

The following table provides comparative results of our operating expenses for the years ended December 31, 2021 and 2020 (in thousands):

	Year Ended December 31,		Increase / (Decrease)	
	2021	2020	$	%
Research and Development Expenses	$205,164	$184,809	20,355	11%
General and Administrative Expenses	37,318	21,864	15,454	71%
Interest (Income)	(363)	(4,329)	(3,966)	(92%)
Other (income)	(273)	(100)	173	173%
	$241,846	$202,244	39,602	20%

Research and Development Expense

Our research and development expenses were $205.2 million for the year ended December 31, 2021 compared to $184.8 million for the year ended December 31, 2020. Research and development expenses increased by $20.4 million in the 2021 period due primarily to the additional activities related to our Phase 3 clinical trials, an increase in headcount, and an increase in stock compensation expense. We expect our research and development expenses to increase as we advance our clinical and preclinical development programs for resmetirom.

General and Administrative Expense

Our general and administrative expenses were $37.3 million for the year ended December 31, 2021 compared to $21.9 million for the year ended December 31, 2020. General and administrative expenses increased by $15.5 million in the 2021 period due primarily to increases in commercial activities, including a corresponding increase in headcount, and an increase in stock compensation expense. We believe our general and administrative expenses may increase over time as we advance our clinical and preclinical development programs for resmetirom, prepare for commercialization, and expand our operating activities, which will likely result in an increase in our headcount, consulting services, and related overhead needed to support those efforts.

Interest Income

Our interest income was $0.4 million for the year ended December 31, 2021 compared to $4.3 million for the year ended December 31, 2020. The decrease in interest income was due primarily to a lower average principal balance in our investment account in 2021 and decreased interest rates.

Liquidity and Capital Resources

Since inception, we have incurred significant net losses and we have funded our operations primarily through the issuance of convertible debt, the issuance of shares of our common stock and shares of our preferred stock, and the proceeds from the merger. Our most significant use of capital pertains to salaries and benefits for our employees, including clinical, scientific, operational, financial and management personnel, and external research and development expenses, such as clinical trials and preclinical activity related to our product candidates.

As of December 31, 2022, we had cash, cash equivalents and marketable securities totaling $358.8 million compared to $270.3 million as of December 31, 2021, with the increase attributable to our fundraising activities, including net proceeds of $155.9 million from our $200 million at-the-market sales agreement entered into in June of 2021, with Cowen and Company, LLC (the "2021 Sales Agreement"), net proceeds of $99.5 million from our registered direct offering ("Registered Direct Offering") of shares of our common stock and Series B Convertible Preferred Stock ("Series B Preferred Stock") in December 2022, and $50.0 million drawn on our Loan Facility, partially offset by cash used in operating activities. Our cash and investment balances are held in a variety of interest-bearing instruments, including obligations of U.S. government agencies, U.S. Treasury debt securities, corporate debt securities and money market funds. Cash in excess of immediate requirements is invested in accordance with our investment policy with a view toward capital preservation and liquidity.

We anticipate continuing to incur operating losses for the foreseeable future. While our rate of cash usage will likely increase in the future, in particular to support our product development and clinical trial efforts, we believe our available cash resources as of December 31, 2022 will be sufficient to fund our operations past one year from the issuance of the financial statements contained herein. Our future long-term liquidity requirements will be substantial and will depend on many factors. To meet future long-term liquidity requirements, as well as maintain compliance with certain of our Loan Facility covenants, we will need to raise additional capital to fund our operations through equity or debt financings, collaborations, partnerships or other strategic transactions. We regularly consider fundraising opportunities and may decide, from time to time, to raise capital based on various factors, including market conditions and our plans of operation. Additional capital may not be available on terms acceptable to us, or at all. We also have the ability to delay certain research activities and related clinical expenses if necessary due to liquidity concerns until a date when those concerns are relieved. If adequate funds are not available, or if the terms of potential funding sources are unfavorable, our business and our ability to develop our product candidates would be harmed. Furthermore, any sales of additional equity securities may result in dilution to our stockholders, and any debt financing may include covenants that restrict our business.

Cash Flows

The following table summarizes our net cash flow activity (in thousands):

	Year Ended December 31,		
	2022	**2021**	**2020**
Net cash used in operating activities	$(224,857)	$(183,917)	$(157,561)
Net cash provided by (used in) investing activities	206,686	(5,055)	159,780
Net cash provided by financing activities	313,451	171,237	5,088
Net increase (decrease) in cash and cash equivalents	$ 295,280	$ (17,735)	$ 7,307

Operating Activities

Net cash used in operating activities was $224.9 million, $183.9 million, and $157.6 million for the years ended December 31, 2022, 2021 and 2020, respectively. The use of cash in these periods resulted primarily from our losses from operations, as adjusted for non-cash charges for stock-based compensation, and changes in our working capital accounts. Net cash used in the year ended December 31, 2022 increased from prior years predominately due to escalated clinical trial related activity.

Investing Activities

Net cash provided by investing activities was $206.7 million for the year ended December 31, 2022 and consisted primarily of $350.4 million from sales and maturities of marketable securities, partially offset by $ $143.5 million of purchase of marketable securities for our investment portfolio.

Net cash used in investing activities was $5.1 million for the year ended December 31, 2021 and consisted primarily of $394.1 million of purchase of marketable securities for our investment portfolio, partially offset by $389.3 million from sales and maturities of marketable securities.

Net cash provided by investing activities was $159.8 million for the year ended December 31, 2020 and consisted primarily of $489.5 million from sales and maturities of marketable securities, partially offset by $329.3 million of purchase of marketable securities for our investment portfolio.

Financing Activities

Net cash provided by financing activities was $313.5 million for the year ended December 31, 2022 and consisted primarily of sales of our common stock under the 2021 Sales Agreement and Registered Direct Offering in December, and debt borrowings under our Loan Facility.

Net cash provided by financing activities was $171.2 million for the year ended December 31, 2021 and consisted primarily of sales of our common stock under the 2021 Sales Agreement and the exercise of stock options.

Net cash provided by financing activities was $5.1 million for the year ended December 31, 2020 and consisted primarily of sales of our common stock under our at-the-market sales agreements with Cowen and Company, LLC and the exercise of stock options.

Contractual Obligations and Commercial Commitments

As of December 31, 2022, we had contractual obligations and commercial commitments as follows (in thousands):

	Payments Due by Period				
Contractual Obligations	**Total**	**Less Than 1 Year**	**1 - 3 Years**	**4 - 5 Years**	**More Than 5 Years**
Operating Leases	622	622	—	—	—
Total contractual Obligations	622	622	—	—	—

Operating leases relate to our corporate headquarters facility located in West Conshohocken, Pennsylvania.

In May 2022 we entered into the $250.0 million Loan Facility with the several banks and other financial institutions or entities party thereto (each, a “Lender” and collectively referred to as the “Lenders”), and Hercules Capital, Inc. (“Hercules”), in its capacity as administrative agent and collateral agent for itself and the Lenders. As of December 31, 2022, we had drawn $50 million under the facility. We are scheduled to pay interest-only monthly payments of accrued interest under the Loan Facility through May 1, 2025, which period may be extended to May 1, 2026 and May 3, 2027 upon the achievement of our regulatory approval milestone and future revenue milestones, and subject to compliance with applicable covenants.

The Company has entered into customary contractual arrangements in support of the Phase 3 clinical trials.

Off-Balance Sheet Arrangements

We do not have any off balance sheet arrangements as defined in Item 303(a)(4)(ii) of Regulation S-K.

Recent Accounting Pronouncements

Refer to Note 2, “Summary of Significant Accounting Policies,” in the accompanying notes to the consolidated financial statements for a discussion of recent accounting pronouncements.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.

Interest Rate Risk

Our exposure to market risk is confined to our cash, cash equivalents and marketable securities. We regularly review our investments and monitor the financial markets. We invest in high-quality financial instruments, primarily money market funds, U.S. government and agency securities, government-sponsored bond obligations and certain other corporate debt securities, with the effective duration of the portfolio less than twelve months and no security with an effective duration in excess of twenty-four months, which we believe are subject to limited credit risk. We currently do not hedge interest rate exposure. Due to the short-term duration of our investment portfolio and the low risk profile of our investments, we believe that an immediate 10% change in interest rates would not have a material effect on the fair market value of our portfolio. We do not believe that we have any material exposure to interest rate risk or changes in credit ratings arising from our investments.

In May 2022 we entered into a Loan Facility that has an interest rate that is linked to the prime rate. We do not believe that we have any material exposure to interest rate risk given the current principal amount of the loan.

Capital Market Risk

We currently have no product revenues and depend on funds raised through other sources. One source of funding is through future debt or equity offerings. Our ability to raise funds in this manner depends upon, among other things, capital market forces affecting our stock price.

Inflation Risk

Inflation has not had a material effect on our business, financial condition or results of operations during the years ended December 31, 2022, 2021 or 2020.

Item 8. Financial Statements and Supplementary Data.

The information required by this Item 8 is referred to in Item 15, listed in the Index to Financial Statements as a part of this Annual Report on Form 10-K, and is incorporated herein by this reference.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure.

None.

Item 9A. Controls and Procedures.

Disclosure Controls and Procedures

We maintain disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act) that are designed to provide reasonable assurance that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our chief executive officer and chief financial officer, as appropriate, to allow timely decisions regarding required disclosure.

Under the supervision of our principal executive officer and principal financial officer, we evaluated the effectiveness of our disclosure controls and procedures as of the end of the period covered by this Report. Based on that evaluation, our principal executive officer and principal financial officer have concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of December 31, 2022.

Limitations on the Effectiveness of Controls and Procedures

In designing and evaluating our disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable, not absolute, assurance of achieving the desired control objectives. In addition, the design of disclosure controls and procedures must reflect the fact that there are resource constraints and that management is required to apply judgment in evaluating the benefits of possible controls and procedures relative to their costs. The design of any disclosure controls and procedures also is based in part upon certain assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions.

Management's Report On Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) for our company. Internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with GAAP. This process includes those policies and procedures that (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of our assets; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with GAAP, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on our financial statements. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Our management, including our principal executive officer and our principal financial officer, assessed the effectiveness of our internal control over financial reporting as of December 31, 2022. In making this assessment, our management used the criteria set forth in the "Internal Control—Integrated Framework" issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework). Based on its assessment under that framework, our management concluded that our internal control over financial reporting was effective as of December 31, 2022.

PricewaterhouseCoopers LLP, an independent registered public accounting firm, has audited the effectiveness of our internal control over financial reporting as of December 31, 2022, as stated in its report, which is included herein.

Changes in Internal Control Over Financial Reporting

There have been no changes in our internal control over financial reporting during the quarter ended December 31, 2022 that have materially affected, or are reasonably likely to materially affect our internal control over financial reporting.

Item 9B. Other Information.

None.

PART III

Certain information required by Part III is omitted from this Annual Report on Form 10-K because we intend to file our definitive Proxy Statement for our next Annual Meeting of Stockholders, pursuant to Regulation 14A of the Securities Exchange Act of 1934, as amended, or the 2023 Proxy Statement, no later than April 30, 2023, and certain information to be included in the 2023 Proxy Statement is incorporated herein by reference.

Item 10. Directors, Executive Officers and Corporate Governance.

The information required by this item concerning our directors, executive officers, Section 16 compliance and corporate governance matters is incorporated by reference in our 2023 Proxy Statement.

Item 11. Executive Compensation.

The information required by this item regarding executive compensation is incorporated by reference in our 2023 Proxy Statement.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters.

The information required by this item regarding security ownership of certain beneficial owners and management is incorporated by reference in our 2023 Proxy Statement. In addition, information about our equity compensation plans is incorporated herein by reference to our 2023 Proxy Statement.

Item 13. Certain Relationships and Related Transactions, and Director Independence.

The information required by this item regarding certain relationships and related transactions is incorporated by reference in our 2023 Proxy Statement.

Item 14. Principal Accountant Fees and Services

The information required by this item regarding principal accounting fees and services is incorporated by reference in our 2023 Proxy Statement.

PART IV

Item 15. **EXHIBITS AND FINANCIAL STATEMENT SCHEDULES**

Item 15(a) The following documents are filed as part of, or incorporated by reference into, this Annual Report on Form 10-K:

Item 15(a)(1) and (2) The Consolidated Financial Statements beginning on page F-1 are filed as part of this Annual Report on Form 10-K. Other financial statement schedules have been omitted because the information required to be presented in them is not applicable or is shown in the financial statements or related notes.

Item 15(a)(3) We have filed, or incorporated into this Annual Report on Form 10-K by reference, the exhibits listed on the accompanying Exhibit Index.

Item 15(b) See Item 15(a)(3) above.

Item 15(c) See Item 15(a)(2) above.

Exhibit Number	Exhibit Description	Filed Herewith	Incorporated by Reference herein from Form or Schedule	Filing Date	SEC File / Registration Number
3.1	Restated Certificate of Incorporation of the Registrant.		Form 10-K (Exhibit 3.1)	3/31/2017	001-33277
3.2	Certificate of Designation of Preferences, Rights and Limitations of Series A Convertible Preferred Stock.		Form 8-K (Exhibit 3.1)	6/21/2017	001-33277
3.3	Certificate of Designation of Preferences, Rights and Limitations of Series B Convertible Preferred Stock		Form 8-K (Exhibit 3.1)	12/23/2022	001-33277
3.4	Bylaws of the Registrant, as amended April 13, 2016.		DEFA14A; Form 8-K (Exhibit 3.1)	4/14/2016	001-33277
4.1	Form of Warrant Agreement, dated May 9, 2022, between the Registrant and Hercules Capital, Inc. and affiliates.		Form 10-Q (Exhibit 4.1)	08/04/2022	001-33277
4.2†	Form of Tranche 2 Warrant Agreement, dated February 3, 2023, by and among the Registrant and Hercules Capital, Inc. and affiliates.		Form 8-K (Exhibit 4.1)	2/9/2023	001-33277
4.3	Description of Securities of the Registrant	X			
Equity Agreements					
10.1	Securities Purchase Agreement, dated June 20, 2017, by and among the Registrant and the investors party thereto, including the Registration Rights Agreement attached as Exhibit B thereto.		Form 8-K (Exhibit 10.1)	6/21/2017	001-33277

Exhibit Number	Exhibit Description	Filed Herewith	Incorporated by Reference herein from Form or Schedule	Filing Date	SEC File / Registration Number
10.2	Amendment No. 2, dated December 22, 2022, to Securities Purchase Agreement, dated June 20, 2017, by and among the Registrant and the investors listed on the signature pages thereto.		Form 8-K (Exhibit 10.2)	12/23/2022	001-33277
10.3	Sales Agreement, dated June 1, 2021, by and between Madrigal Pharmaceuticals, Inc. and Cowen and Company, LLC (concerning at-the-market offerings of Madrigal common stock).		Form 8-K (Exhibit 1.1)	6/1/2021	001-33277
10.4	Securities Purchase Agreement, dated December 21, 2022, by and among the Registrant and the institutional investors listed on the signature pages thereto.		Form 8-K (Exhibit 10.1)	12/23/2022	001-33277
Debt Agreements					
10.5†	Loan and Security Agreement, dated May 9, 2022, by and among the Registrant, Canticle Pharmaceuticals, Inc., the several banks and other financial institutions or entities from time to time party thereto and Hercules Capital, Inc.		Form 10-Q (Exhibit 10.1)	8/4/2022	001-33277
10.6†	Loan and Security Agreement, dated May 9, 2022, as amended by the First Amendment to Loan and Security Agreement, dated February 3, 2023, by and among the Registrant, Canticle Pharmaceuticals, Inc., the several banks and other financial institutions or entities from time to time party thereto and Hercules Capital, Inc.		Form 8-K (Exhibit 10.1)	2/09/2023	001-33277
Agreements with Respect to Collaborations, Licenses, Research and Development					
10.7	Research, Development and Commercialization Agreement, dated December 18, 2008, by and between Hoffmann-La Roche, Inc., F. Hoffmann-La Roche Ltd and the Registrant.†		Form 10-Q (Exhibit 10.5)	11/14/2016	001-33277
Equity Compensation Plans					
10.8*	Amended 2015 Stock Plan		Definitive Proxy Statement (Annex A)	4/30/2021	001-33277
10.9*	Form of Incentive Stock Option Agreement under Amended 2015 Stock Plan.		Form 10-K (Exhibit 10.10)	3/31/2017	001-33277

Exhibit Number	Exhibit Description	Filed Herewith	Incorporated by Reference herein from Form or Schedule	Filing Date	SEC File / Registration Number
10.10*	Form of Nonqualified Stock Option Agreement under Amended 2015 Stock Plan.		Form 10-K (Exhibit 10.11)	3/31/2017	001-33277
10.11*	Form of Nonqualified Stock Option Agreement for Directors under Amended 2015 Stock Plan.		Form 10-K (Exhibit 10.13)	3/31/2017	001-33277
10.12*	Form of Restricted Stock Unit Agreement under Amended 2015 Stock Plan.	X			
10.13*	Non-Employee Director Equity Compensation Policy		Form 10-Q (Exhibit 10.1)	5/6/2021	001-33277
Agreements with Executive Officers and Directors					
10.14*	Form of Indemnification Agreement between the Registrant and certain directors and executive officers.		Form 8-K (Exhibit 10.2)	7/22/2016	001-33277
10.15*	Letter Agreement, dated April 13, 2016, by and between the Company and Paul A. Friedman, M.D.		Form 8-K (Exhibit 10.3)	7/22/2016	001-33277
10.16*	Letter Agreement, dated April 13, 2016, by and between the Company and Rebecca Taub, M.D.		Form 8-K (Exhibit 10.4)	7/22/2016	001-33277
21.1	List of Subsidiaries.	X			
23.1	Consent of PricewaterhouseCoopers LLP, Independent Registered Public Accounting Firm.	X			
31.1	Certification of Principal Executive Officer required by Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.	X			
31.2	Certification of Principal Financial Officer pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.	X			
32.1**	Certifications of Principal Executive Officer and Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.	X			
101.INS	Inline XBRL Instance Document.	X			
101.SCH	Inline XBRL Taxonomy Extension Schema Document.	X			

Exhibit Number	Exhibit Description	Filed Herewith	Incorporated by Reference herein from Form or Schedule	Filing Date	SEC File / Registration Number
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document.	X			
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document.	X			
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document.	X			
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document.	X			
104	Inline XBRL for the cover page of this Annual Report on Form 10-K, included in the Exhibit 101 Inline XBRL Document Set.	X			

* Indicates a management contract, compensatory plan or arrangement.

** The certifications attached as Exhibit 32.1 that accompany this Annual Report on Form 10-K are not deemed filed with the SEC and are not to be incorporated by reference into any filing of the registrant under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, whether made before or after the date of this Annual Report on Form 10-K, regardless of any general incorporation language contained in any filing.

† Certain portions of this exhibit have been omitted pursuant to Item 601(b)(10)(iv) of Regulation S-K.

Item 16. Form 10-K Summary.

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this Report to be signed on its behalf by the undersigned thereunto duly authorized.

MADRIGAL PHARMACEUTICALS INC.

Date: February 23, 2023

By: /s/ PAUL A. FRIEDMAN, M.D.
Paul A. Friedman, M.D.
Chief Executive Officer
(Principal Executive Officer)

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each individual whose signature appears below hereby constitutes and appoints Paul A. Friedman, M.D., Alex G. Howarth and Brian J. Lynch, and each or either of them, acting individually, as his or her true and lawful attorney-in-fact and agent, with full power of substitution and resubstitution for him or her and in his or her name, place and stead, in any and all capacities, to sign any and all amendments to this Report, and to file the same, with all exhibits thereto and other documents in connection therewith, with the SEC, granting unto said attorney-in-fact and agent, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully for all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorney-in-fact and agent, or any of them, or their or his or her substitutes, may lawfully do or cause to be done or by virtue hereof.

Pursuant to the requirements of the Exchange Act, as amended, this Report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signatures	Title	Date
/s/ PAUL A. FRIEDMAN, M.D. Paul A. Friedman, M.D.	Chairman of the Board of Directors and Chief Executive Officer (Principal Executive Officer)	February 23, 2023
/s/ ALEX G. HOWARTH Alex G. Howarth	Chief Financial Officer (Principal Accounting and Financial Officer)	February 23, 2023
/s/ REBECCA TAUB, M.D. Rebecca Taub, M.D.	Director	February 23, 2023
/s/ FRED B. CRAVES, PH.D. Fred B. Craves, Ph.D.	Director	February 23, 2023
/s/ KENNETH M. BATE Kenneth M. Bate	Director	February 23, 2023
/s/ KEITH R. GOLLUST Keith R. Gollust	Director	February 23, 2023

Signatures	Title	Date
/s/ DAVID MILLIGAN, PH.D. David Milligan, Ph.D.	Director	February 23, 2023
/s/ RICHARD S. LEVY, M.D. Richard S. Levy, M.D.	Director	February 23, 2023
/s/ JAMES M. DALY James M. Daly	Director	February 23, 2023

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Board of Directors and Stockholders of Madrigal Pharmaceuticals, Inc.

Opinions on the Financial Statements and Internal Control over Financial Reporting

We have audited the accompanying consolidated balance sheets of Madrigal Pharmaceuticals, Inc. and its subsidiaries (the "Company") as of December 31, 2022 and 2021, and the related consolidated statements of operations, of comprehensive loss, of stockholders' equity and of cash flows for each of the three years in the period ended December 31, 2022, including the related notes (collectively referred to as the "consolidated financial statements"). We also have audited the Company's internal control over financial reporting as of December 31, 2022, based on criteria established in Internal Control—Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO).

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of the Company as of December 31, 2022 and 2021, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2022 in conformity with accounting principles generally accepted in the United States of America. Also in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2022, based on criteria established in Internal Control—Integrated Framework (2013) issued by the COSO.

Basis for Opinions

The Company's management is responsible for these consolidated financial statements, for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting, included in Management's Report On Internal Control Over Financial Reporting appearing under Item 9A. Our responsibility is to express opinions on the Company's consolidated financial statements and on the Company's internal control over financial reporting based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud, and whether effective internal control over financial reporting was maintained in all material respects.

Our audits of the consolidated financial statements included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits provide a reasonable basis for our opinions.

Emphasis of Matter

As discussed in Note 3 to the consolidated financial statements, the Company will require additional financing to fund future operations. Management's evaluation of the events and conditions and plans to mitigate this matter are also described in Note 3.

Definition and Limitations of Internal Control over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Critical Audit Matters

The critical audit matter communicated below is a matter arising from the current period audit of the consolidated financial statements that was communicated or required to be communicated to the audit committee and that (i) relates to accounts or disclosures that are material to the consolidated financial statements and (ii) involved our especially challenging, subjective, or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Research and Development Costs

As described in Notes 2 and 5 to the consolidated financial statements, management uses significant judgment in estimating the amount of research and development costs recognized in each reporting period. Management analyzes and estimates the progress of its preclinical studies and clinical trials, completion of milestone events per underlying agreements, invoices received and contracted costs when estimating the research and development costs to accrue in each reporting period. Total research and development costs incurred during the year ended December 31, 2022 were $245.4 million and research and development costs accrued were $53.1 million as of December 31, 2022. The principal considerations for our determination that performing procedures relating to research and development costs is a critical audit matter are (i) the significant judgment by management when estimating: the costs incurred for services performed by vendors that have not yet been invoiced, the completion of milestone events per underlying agreements, and invoices received and contracted costs, in estimating the research and development costs to accrue in the reporting period; and (ii) the high degree of auditor judgment, subjectivity and effort in evaluating management's significant assumption related to using contracted costs applied to the number of patients screened for and enrolled in the trials to reasonably estimate costs incurred that have not been invoiced.

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Addressing the matter involved performing procedures and evaluating audit evidence in connection with forming our overall opinion on the consolidated financial statements. These procedures included testing the effectiveness of controls over management's process relating to accruing research and development costs, including controls over estimating the costs incurred for services performed by vendors that have not yet been invoiced. These procedures also included, among others, testing management's process for estimating the research and development costs to accrue in the reporting period, evaluating the completeness and accuracy of underlying data used in management's estimate by testing for consistency with a sample of contracts and invoices, testing the number of patients screened for and enrolled in the trial, testing the mathematical accuracy of the calculation of the accrual for research and development costs incurred, and evaluating the reasonableness of assumptions used in the estimate. Evaluating the reasonableness of assumptions used in the estimate involved assessing management's ability to reasonably estimate costs incurred that have not been invoiced by performing a comparison of the estimated accrual to contracted costs applied to the number of patients screened for and enrolled in the trials.

/s/ PricewaterhouseCoopers LLP
Philadelphia, Pennsylvania
February 23, 2022

We have served as the Company's auditor since 2016.

MADRIGAL PHARMACEUTICALS, INC.

Consolidated Balance Sheets

(in thousands, except share and per share amounts)

	December 31, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 331,549	$ 36,269
Marketable securities	27,225	234,077
Prepaid expenses and other current assets	2,595	1,338
Total current assets	361,369	271,684
Property and equipment, net	601	851
Right-of-use asset	602	797
Total assets	$ 362,572	$ 273,332
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 23,831	$ 21,380
Accrued expenses	91,461	55,048
Lease liability	602	410
Total current liabilities	115,894	76,838
Long term liabilities:		
Loan payable, net of discount	49,289	—
Lease liability	—	387
Total long term liabilities	49,289	387
Total liabilities	165,183	77,225
Stockholders' equity:		
Preferred stock, par value $0.0001 per share authorized: 5,000,000 shares at December 31, 2022 and December 31, 2021; 2,369,797 and 1,969,797 shares issued and outstanding at December 31, 2022 and December 31, 2021, respectively	—	—
Common stock, par value $0.0001 per share authorized: 200,000,000 at December 31, 2022 and December 31, 2021; 18,102,523 and 17,103,395 shares issued and outstanding at December 31, 2022 and December 31, 2021, respectively	2	2
Additional paid-in-capital	1,160,079	863,495
Accumulated other comprehensive loss	(32)	(80)
Accumulated deficit	(962,660)	(667,310)
Total stockholders' equity	197,389	196,107
Total liabilities and stockholders' equity	$ 362,572	$ 273,332

See accompanying notes to consolidated financial statements.

MADRIGAL PHARMACEUTICALS, INC.

Consolidated Statements of Operations

(in thousands, except share and per share amounts)

	Year Ended December 31,		
	2022	2021	2020
Revenues:			
Total revenues	$ —	$ —	$ —
Operating expenses:			
Research and development	245,441	205,164	184,809
General and administrative	48,130	37,318	21,864
Total operating expenses	293,571	242,482	206,673
Loss from operations	(293,571)	(242,482)	(206,673)
Interest income	2,185	363	4,329
Interest expense	(3,964)	—	—
Other income	—	273	100
Net loss	$ (295,350)	$ (241,846)	$ (202,244)
Net loss per common share:			
Basic and diluted net loss per common share	$ (17.23)	$ (14.63)	$ (13.09)
Basic and diluted weighted average number of common shares outstanding	17,137,201	16,535,188	15,446,638

See accompanying notes to consolidated financial statements.

MADRIGAL PHARMACEUTICALS, INC.

Consolidated Statements of Comprehensive Loss

(in thousands, except share and per share amounts)

	Year Ended December 31,		
	2022	2021	2020
Net Loss	$ (295,350)	$ (241,846)	$ (202,244)
Other comprehensive income (loss):			
Unrealized gain (loss) on available-for-sale securities	48	(127)	(169)
Comprehensive loss	$ (295,302)	$ (241,973)	$ (202,413)

See accompanying notes to consolidated financial statements.

MADRIGAL PHARMACEUTICALS, INC.

Consolidated Statements of Stockholders' Equity

(in thousands, except share and per share amounts)

	Preferred stock		Common stock		Additional paid-in Capital	Accumulated other comprehensive income (loss)	Accumulated deficit	Total stockholders' equity
	Shares	Amount	Shares	Amount				
Balance at December 31, 2019	1,969,797	$ —	15,429,154	$ 2	$ 639,567	$ 216	$(223,220)	$ 416,565
Issuance of common shares in equity offering, excluding to related parties, net of transaction costs	—	—	39,607	—	4,421	—	—	4,421
Sale of common shares to related parties and exercise of common stock options, net of transaction costs	—	—	39,385	—	667	—	—	667
Compensation expense related to stock options for services	—	—	—	—	20,730	—	—	20,730
Unrealized loss on marketable securities	—	—	—	—	—	(169)	—	(169)
Net loss	—	—	—	—	—	—	(202,244)	(202,244)
Balance at December 31, 2020	1,969,797	$ —	15,508,146	$ 2	$ 665,385	$ 47	$(425,464)	$ 239,970
Issuance of common shares in equity offering, excluding to related parties, net of transaction costs	—	—	1,584,169	—	170,207	—	—	170,207
Sale of common shares to related parties and exercise of common stock options, net of transaction costs	—	—	11,080	—	1,030	—	—	1,030
Compensation expense related to stock options for services	—	—	—	—	26,873	—	—	26,873
Unrealized loss on marketable securities	—	—	—	—	—	(127)	—	(127)
Net loss	—	—	—	—	—	—	(241,846)	(241,846)
Balance at December 31, 2021	1,969,797	$ —	17,103,395	$ 2	$ 863,495	$ (80)	$(667,310)	$ 196,107
Issuance of common and preferred shares in equity offerings, excluding to related parties, net of transaction costs	400,000	—	783,344	—	255,382	—	—	255,382
Sale of common shares to related parties and exercise of common stock options, net of transaction costs	—	—	215,784	—	8,955	—	—	8,955
Compensation expense related to stock options for services	—	—	—	—	31,625	—	—	31,625
Unrealized loss on marketable securities	—	—	—	—	—	48	—	48
Hercules warrant	—	—	—	—	622	—	—	622
Net loss	—	—	—	—	—	—	(295,350)	(295,350)
Balance at December 31, 2022	2,369,797	$ —	18,102,523	$ 2	$1,160,079	$ (32)	$(962,660)	$ 197,389

See accompanying notes to consolidated financial statements.

MADRIGAL PHARMACEUTICALS, INC.

Consolidated Statements of Cash Flows

(in thousands, except share and per share amounts)

	Year Ended December 31,		
	2022	2021	2020
Cash flows from operating activities:			
Net loss	$ (295,350)	$ (241,846)	$ (202,244)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense	31,625	26,873	20,730
Depreciation and amortization expense	467	405	471
Amortization of debt issuance costs and discount	797	—	—
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	(1,257)	(325)	138
Accounts payable	2,451	20,363	(161)
Accrued expense	36,413	9,826	21,585
Accrued interest, net of interest received on maturity of investments	(3)	787	1,920
Net cash used in operating activities	(224,857)	(183,917)	(157,561)
Cash flows from investing activities:			
Purchases of marketable securities	(143,478)	(394,120)	(329,342)
Sales and maturities of marketable securities	350,381	389,274	489,456
Purchases of property and equipment, net of disposals	(217)	(209)	(334)
Net cash provided by (used in) investing activities	206,686	(5,055)	159,780
Cash flows from financing activities:			
Proceeds from issuances of stock, excluding related parties, net of transaction costs	255,382	170,207	4,421
Proceeds from the sale of related party stock and exercise of common stock options, net of transaction costs	8,955	1,030	667
Proceeds from issuance of loan payable	50,000	—	—
Payment of debt issuance costs	(886)	—	—
Net cash provided by financing activities	313,451	171,237	5,088
Net increase (decrease) in cash and cash equivalents	295,280	(17,735)	7,307
Cash and cash equivalents at beginning of period	36,269	54,004	46,697
Cash and cash equivalents at end of period	$ 331,549	$ 36,269	$ 54,004
Supplemental disclosure of cash flow information:			
Obtaining a right-of-use asset in exchange for a lease liability	$ 583	$ 376	$ 451

See accompanying notes to consolidated financial statements.

MADRIGAL PHARMACEUTICALS, INC.

Notes to Consolidated Financial Statements

1. Organization, Business and Basis of Presentation

Organization and Business

Madrigal Pharmaceuticals, Inc. (the "Company" or "Madrigal") is a clinical-stage pharmaceutical company developing novel, high-quality, small-molecule drugs addressing major unmet needs in cardiovascular, metabolic, and liver diseases. The Company's lead compound, resmetirom, is being advanced for non-alcoholic steatohepatitis ("NASH"), a liver disease that commonly affects people with metabolic diseases such as obesity and diabetes, and non-alcoholic fatty liver disease ("NAFLD"). The Company initiated two Phase 3 studies of resmetirom in NASH in 2019 that are ongoing. The Company announced certain topline results from the MAESTRO-NAFLD-1 safety study of resmetirom in January 2022 and the MAESTRO-NASH study in December 2022. In August 2022, Madrigal initiated a third study, MAESTRO-NASH-OUTCOMES.

Certain prior period amounts have been reclassified to align with current period presentation.

2. Summary of Significant Accounting Policies

Principle of Consolidation

The consolidated financial statements include the financial statements of the Company and its wholly owned subsidiaries. All significant intercompany balances and transactions have been eliminated in consolidation.

Use of Estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect certain reported amounts of assets and liabilities, and the reported amounts of revenues and expenses during the reporting periods. The Company bases its estimates on historical experience and various other assumptions that management believes to be reasonable under the circumstances. Changes in estimates are recorded in the period in which they become known. Actual results could differ from those estimates.

Cash and Cash Equivalents

The Company considers all highly liquid investments with original maturities of three months or less at the date of purchase to be cash equivalents. The Company maintains its cash in bank accounts, the balance of which, at times, exceeds Federal Deposit Insurance Corporation insured limits.

The primary objective of the Company's investment activities is to preserve its capital for the purpose of funding operations and the Company does not enter into investments for trading or speculative purposes. The Company's cash is deposited in highly rated financial institutions in the United States. The Company invests in money market funds and high-grade, commercial paper and corporate bonds, which management believes are subject to minimal credit and market risk.

Marketable Securities

Marketable securities consist of investments in high-grade corporate obligations, and government and government agency obligations that are classified as available-for-sale. Since these securities are available to fund current operations they are classified as current assets on the consolidated balance sheets.

The Company adjusts the cost of available-for-sale debt securities for amortization of premiums and accretion of discounts to maturity. The Company includes such amortization and accretion as a component of interest income, net. Realized gains and losses and declines in value, if any, that the Company judges to be the result of impairment or as a result of recognizing an allowance for credit losses on available-for-sale securities are reported as a component of interest income. To determine whether an impairment exists, the Company considers whether it intends to sell the debt security and, if the Company does not intend to sell the debt security, it considers available evidence to assess whether it is more likely than not that it will be required to sell the security before the recovery of its amortized cost basis. During the years ended December 31, 2022, 2021 and 2020, the Company determined it did not have any securities that were impaired or that required an allowance for credit losses.

Marketable securities are stated at fair value, including accrued interest, with their unrealized gains and losses included as a component of accumulated other comprehensive income or loss, which is a separate component of stockholders' equity. The fair value of these securities is based on quoted prices and observable inputs on a recurring basis. Realized gains and losses are determined on the specific identification method. During the years ended December 31, 2022, 2021 and 2020, the Company did not have any realized gains or losses on marketable securities.

Fair Value of Financial Instruments

The carrying amounts of the Company's financial instruments, which include cash equivalents, and marketable securities, approximate their fair values. The fair value of the Company's financial instruments reflects the amounts that would be received upon sale of an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. The fair value hierarchy has the following three levels:

Level 1—quoted prices in active markets for identical assets and liabilities.

Level 2—observable inputs other than Level 1 inputs. Examples of Level 2 inputs include quoted prices in active markets for similar assets or liabilities and quoted prices for identical assets or liabilities in markets that are not active.

Level 3—unobservable inputs that reflect the Company's own assumptions about the assumptions market participants would use in pricing the asset or liability.

Financial assets and liabilities are classified in their entirety within the fair value hierarchy based on the lowest level of input that is significant to the fair value measurement. The Company measures the fair value of its marketable securities by taking into consideration valuations obtained from third-party pricing sources. The pricing services utilize industry standard valuation models, including both income and market-based approaches, for which all significant inputs are observable, either directly or indirectly, to estimate fair value. These inputs include reported trades of and broker-dealer quotes on the same or similar securities, issuer credit spreads, benchmark securities and other observable inputs.

As of December 31, 2022 and 2021, the Company's financial assets valued based on Level 1 inputs consisted of cash and cash equivalents in a money market fund and its financial assets valued based on Level 2 inputs consisted of high-grade corporate bonds and commercial paper. During the years ended December 31, 2022, 2021 and 2020, the Company did not have any transfers of financials assets between Levels 1 and 2. As of December 31, 2022 and 2021, the Company did not have any financial liabilities that were recorded at fair value on a recurring basis on the balance sheet.

Research and Development Costs

Research and development costs are expensed as incurred. Research and development costs are comprised of costs incurred in performing research and development activities, including internal costs (including

stock-based compensation), costs for consultants, milestone payments under licensing agreements, and other costs associated with the Company's preclinical and clinical programs. In particular, the Company has conducted safety studies in animals, optimized and implemented the manufacturing of our drug, and conducted Phase 1-3 clinical trials, all of which are considered research and development expenditures. Management uses significant judgment in estimating the amount of research and development costs recognized in each reporting period. Management analyzes and estimates the progress of its preclinical studies and clinical trials, completion of milestones events per underlying agreements, invoices received and contracted costs when estimating the research and development costs to accrue in each reporting period. Actual results could differ from the Company's estimates. The Company's historical estimates for research and development costs have not been materially different from the actual costs.

Patents

Costs to secure and defend patents are expensed as incurred and are classified as general and administrative expense in the Company's statements of operations. Patent expenses were approximately $0.5 million, $0.5 million and $0.4 million for the years ended December 31, 2022, 2021 and 2020, respectively.

Stock-Based Compensation

The Company recognizes stock-based compensation expense based on the grant date fair value of stock options granted to employees, officers and directors. The Company uses the Black-Scholes option pricing model to determine the grant date fair value as management believes it is the most appropriate valuation method for its option grants. The Black-Scholes model requires inputs for risk-free interest rate, dividend yield, volatility and expected lives of the options. The expected lives for options granted represent the period of time that options granted are expected to be outstanding. The Company uses the simplified method for determining the expected lives of options. Expected volatility is based upon an industry estimate or blended rate including the Company's historical trading activity. The risk-free rate for periods within the expected life of the option is based on the U.S. Treasury yield curve in effect at the time of the grant. The Company estimates the forfeiture rate based on historical data. This analysis is re-evaluated at least annually and the forfeiture rate is adjusted as necessary.

Certain of the employee stock options granted by the Company are structured to qualify as incentive stock options (ISOs). Under current tax regulations, the Company does not receive a tax deduction for the issuance, exercise or disposition of ISOs if the employee meets certain holding requirements. If the employee does not meet the holding requirements, a disqualifying disposition occurs, at which time the Company may receive a tax deduction. The Company does not record tax benefits related to ISOs unless and until a disqualifying disposition is reported. In the event of a disqualifying disposition, the entire tax benefit is recorded as a reduction of income tax expense. The Company has not recognized any income tax benefit for its share-based compensation arrangements due to the fact that the Company does not believe it is more likely than not it will realize the related deferred tax assets.

Income Taxes

The Company uses the asset and liability method to account for income taxes. Deferred tax assets and liabilities are determined based on the expected future tax consequences of temporary differences between the Company's financial statement carrying amounts and the tax basis of assets and liabilities using enacted tax rates expected to be in effect in the years in which the differences are expected to reverse. The Company currently maintains a 100% valuation allowance on its deferred tax assets.

Comprehensive Loss

Comprehensive loss is defined as the change in equity of a business enterprise during a period from transactions and other events and circumstances from non-owner sources. Changes in unrealized gains and losses on marketable securities represent the only difference between the Company's net loss and comprehensive loss.

Basic and Diluted Loss Per Common Share

Basic net loss per share is computed using the weighted average number of common shares outstanding during the period, excluding restricted stock that has been issued but is not yet vested. Diluted net loss per common share is computed using the weighted average number of common shares outstanding and the weighted average dilutive potential common shares outstanding using the treasury stock method. However, for the years ended December 31, 2022, 2021 and 2020, diluted net loss per share is the same as basic net loss per share because the inclusion of common stock issuable upon the exercise of stock options or warrants, and common stock issuable upon the conversion of preferred stock would be anti-dilutive. The following table summarizes outstanding securities not included in the computation of diluted net loss per common share as their inclusion would be anti-dilutive:

	As of December 31,		
	2022	2021	2020
Common stock options	2,857,054	2,301,574	1,837,540
Preferred stock	2,369,797	1,969,797	1,969,797
Warrants	14,899	—	—

Recent Accounting Pronouncements

None.

3. Liquidity and Uncertainties

The Company is subject to risks common to development stage companies in the biopharmaceutical industry including, but not limited to, uncertainty of product development and commercialization, dependence on key personnel, uncertainty of market acceptance of products and product reimbursement, product liability, uncertain protection of proprietary technology, potential inability to raise additional financing necessary for development and commercialization, and compliance with the U.S. Food and Drug Administration and other government regulations.

The Company has incurred losses since inception, including approximately $295.4 million for the year ended December 31, 2022, resulting in an accumulated deficit of approximately $962.7 million and $667.3 million as of December 31, 2022 and 2021, respectively. Management expects to incur losses for the foreseeable future. To date, the Company has funded its operations primarily through proceeds from sales of the Company's capital stock. The Company believes that its cash, cash equivalents and marketable securities at December 31, 2022 will be sufficient to fund operations past one year from the issuance of these financial statements. To meet its future capital needs, the Company intends to raise additional capital through debt or equity financings, collaborations, partnerships or other strategic transactions. However, there can be no assurance that the Company will be able to complete any such transactions on acceptable terms or otherwise. The inability of the Company to obtain sufficient funds on acceptable terms when needed could have a material adverse effect on the Company's business, results of operations and financial condition. The Company has the ability to delay certain research activities and related clinical expenses if necessary due to liquidity concerns until a date when those concerns are relieved.

4. Cash, Cash Equivalents and Marketable Securities

A summary of cash, cash equivalents and available-for-sale marketable securities held by the Company as of December 31, 2022 and 2021 is as follows (in thousands):

	December 31, 2022			
	Cost	Unrealized gains	Unrealized losses	Fair value
Cash and cash equivalents:				
Cash (Level 1)	$ 15,100	$ —	$ —	$ 15,100
Money market funds (Level 1)	316,449	—	—	316,449
Total cash and cash equivalents	331,549	—	—	331,549
Marketable securities:				
Corporate debt securities due within 1 year of date of purchase (Level 2)	27,257	7	(39)	27,225
Total cash, cash equivalents and marketable securities	$358,806	$ 7	$ (39)	$358,774

	December 31, 2021			
	Cost	Unrealized gains	Unrealized losses	Fair value
Cash and cash equivalents:				
Cash (Level 1)	$ 18,877	$ —	$ —	$ 18,877
Money market funds (Level 1)	17,392	—	—	17,392
Total cash and cash equivalents	36,269	—	—	36,269
Marketable securities:				
Corporate debt securities due within 1 year of date of purchase (Level 2)	228,348	6	(66)	228,288
Corporate debt securities due within 1 to 2 years of date of purchase (Level 2)	5,809	—	(20)	5,789
Total cash, cash equivalents and marketable securities	$270,426	$ 6	$ (86)	$270,346

5. Accrued Liabilities

Accrued liabilities as of December 31, 2022 and 2021 consisted of the following (in thousands):

	December 31, 2022	December 31, 2021
Contract research organization costs	$ 53,119	$ 38,349
Other clinical study related costs	6,582	3,957
Manufacturing and drug supply	11,262	3,239
Compensation and benefits	14,864	6,769
Professional fees	4,867	2,455
Other	767	279
Total accrued liabilities	$ 91,461	$ 55,048

6. Long Term Debt

In May 2022 the Company and its wholly-owned subsidiary, Canticle Pharmaceuticals, Inc., entered into the $250.0 million Loan Facility (the "Loan Facility") with the several banks and other financial institutions or entities party thereto (each, a "Lender" and collectively referred to as the "Lenders"), and Hercules Capital, Inc.

("Hercules"), in its capacity as administrative agent and collateral agent for itself and the Lenders. Under the terms of the Loan Facility, the first $50.0 million tranche was drawn at closing. The Company may also draw up to an additional $125.0 million in two separate tranches upon achievement of certain resmetirom clinical and regulatory milestones. A fourth tranche of $75.0 million may be drawn by the Company, subject to the approval of Hercules.

The Loan Facility had a minimum interest rate of 7.45% and adjusted with changes in the prime rate. The Company will pay interest-only monthly payments of accrued interest under the Loan Facility through May 1, 2025, for a period of 36 months, which period may be extended to May 1, 2026 and May 3, 2027, upon the achievement of regulatory approval milestones and future revenue covenants, subject to compliance with applicable covenants. The Loan Facility matures in May 2026 and may be extended an additional year upon the achievement of certain regulatory milestones. The Loan Facility is secured by a security interest in substantially all of the Company's assets, other than intellectual property. It includes an end of term charge of 5.35% of the aggregate principal amount, which is accounted for in the loan discount. In connection with the first tranche drawn at closing, the Company issued Hercules a warrant to purchase 14,899 shares of Company common stock, which had a Black-Scholes value of $0.6 million.

The Loan Facility includes affirmative and restrictive financial covenants commencing on January 1, 2023, including maintenance of a minimum cash, cash equivalents and liquid funds covenant of $35.0 million, which may decrease in certain circumstances if the Company achieves certain clinical milestones and a revenue milestone, and a revenue-based covenant that could apply commencing at or after the time that financial reporting is due for the quarter ending September 30, 2024. The Loan Facility contains event of default provisions for: the Company's failure to make required payments or maintain compliance with covenants under the Loan Facility; the Company's breach of certain representations or default under certain obligations outside the Loan Facility; insolvency, attachment or judgment events affecting the Company; and any circumstance which has occurred or could reasonably be expected to have a material adverse effect on the Company, provided that, any failure to achieve approval or certain other milestones under the Loan Facility shall not in and of itself constitute a material adverse effect. The Loan Facility also includes customary covenants associated with a secured loan facility, including covenants concerning financial reporting obligations, and certain limitations on indebtedness, liens (including a negative pledge on intellectual property and other assets), investments, distributions (including dividends), collateral, investments, distributions, transfers, mergers or acquisitions, taxes, corporate changes, and deposit accounts.

As of December 31, 2022, the outstanding principal under the Loan Facility was $50.0 million. The interest rate as of December 31, 2022 was 11.45%. As of December 31, 2022, the Company was in compliance with all loan covenants and provisions.

Future minimum payments, including interest and principal, under the loans payable outstanding as of December 31, 2022 are as follows (in thousands):

Period Ending December 31, 2022:	Amount
2023	$ 5,795
2024	5,820
2025	34,788
Thereafter	23,272
	$ 69,675
Less amount representing interest	(17,000)
Less unamortized discount	(3,386)
Loans payable, net of discount	$ 49,289

See Footnote 13 for a description of certain amended terms set forth in the First Amendment to this Loan Facility, which was entered into during the first quarter of 2023.

7. Stockholders' Equity

Common Stock

Each common stockholder is entitled to one vote for each share of common stock held. The common stock will vote together with all other classes and series of stock of the Company as a single class on all actions to be taken by the Company's stockholders. Each share of common stock is entitled to receive dividends, as and when declared by the Company's board of directors.

The Company has never declared cash dividends on its common stock and does not expect to do so in the foreseeable future.

Preferred Stock

The Series A and B Preferred Stock have a par value of $0.0001 per share and are convertible into shares of the common stock at a one-to-one ratio, subject to adjustment as provided in the Certificates of Designation of Preferences, Rights and Limitations of Series A Preferred Stock and Series B Preferred Stock that the Company filed with the Secretary of State of the State of Delaware on June 21, 2017 and December 22, 2022, respectively. The terms of the Series A and B Preferred Stock are set forth in such Certificates of Designation. Each share of the Series A and B Preferred Stock is convertible into shares of Common Stock following notice that may be given at the holder's option. Upon any liquidation, dissolution or winding-up of the Company, whether voluntary or involuntary, after the satisfaction in full of the debts of the Company and the payment of any liquidation preference owed to the holders of shares of capital stock of the Company ranking prior to the Series A and B Preferred Stock upon liquidation, the holders of the Series A and B Preferred Stock shall participate pari passu with the holders of the Common Stock (on an as-if-converted-to-Common-Stock basis) in the net assets of the Company. Shares of the Series A and B Preferred Stock will generally have no voting rights, except as required by law. Shares of the Series A and B Preferred Stock will be entitled to receive dividends before shares of any other class or series of capital stock of the Company (other than dividends in the form of the Common Stock) equal to the dividend payable on each share of the Common Stock, on an as-converted basis.

December 2022 Registered Direct Offering

In December 2022, the Company entered into a Securities Purchase Agreement (the "Purchase Agreement") with a group of institutional accredited investors, who were existing, non-controlling stockholders of the Company, pursuant to which the Company sold securities to the Investors in an offering that was registered under the Company's existing shelf registration statement (the "2022 Registered Direct Offering"). Under the terms of the Purchase Agreement, the Company sold 44,444 shares of its common stock at a price of $225 per share, and 400,000 shares of its Series B Convertible Preferred Stock at a price of $225 per share. The 2022 Registered Direct Offering resulted in gross proceeds to the Company of approximately $100.0 million, and net proceeds to the Company of approximately $99.5 million. The 2022 Registered Direct Offering closed on December 23, 2022.

At-The-Market Issuance Sales Agreement

In November 2020, the Company entered into an at-the-market sales agreement (the "2020 Sales Agreement"), with Cowen and Company, LLC ("Cowen"), pursuant to which the Company could, from time to time, issue and sell shares of its common stock. The 2020 Sales Agreement authorized an aggregate offering of up to $200 million in shares of our common stock, at the Company's option, through Cowen as its sales agent. Sales of common stock through Cowen could be made by any method that is deemed an "at-the-market" offering as defined in Rule 415 promulgated under the Securities Act of 1933, as amended, including by means of ordinary brokers' transactions at market prices, in block transactions or as otherwise agreed by the Company and Cowen. The 2020 Sales Agreement was terminated in June 2021 when the Company filed a new shelf registration statement.

Under the 2020 Sales Agreement the Company sold 1,126,733 shares for an aggregate of approximately $137.4 million in gross proceeds, with net proceeds to the Company of approximately $134.8 million after deducting commissions and other transaction costs. Of those shares sold, 1,087,126 were sold in 2021, and 39,607 were sold in 2020.

In June 2021, the Company entered into an at-the-market sales agreement (the "2021 Sales Agreement") with Cowen and Company, LLC ("Cowen"), pursuant to which the Company could, from time to time, issue and sell shares of its common stock. The 2021 Sales Agreement authorized an aggregate offering of up to $200 million in shares of our common stock, at the Company's option, through Cowen as its sales agent. Sales of common stock through Cowen could be made by any method that is deemed an "at-the-market" offering as defined in Rule 415 promulgated under the Securities Act of 1933, as amended, including by means of ordinary brokers' transactions at market prices, in block transactions or as otherwise agreed by the Company and Cowen. Subject to the terms and conditions of the 2021 Sales Agreement, Cowen would use commercially reasonable efforts consistent with its normal trading and sales practices to sell the common stock based upon the Company's instructions (including any price, time or size limits or other customary parameters or conditions the Company imposed).The 2021 Sales Agreement replaced the 2020 Sales Agreement.

In December 2022, the Company sold 738,900 shares under the 2021 Sales Agreement for an aggregate of $159.1 million in gross proceeds, with net proceeds to the Company of $155.9 million after deducting commissions and other transaction costs.

In total, under the 2021 Sales Agreement the Company sold 1,235,943 shares for an aggregate of $199.9 million in gross proceeds, with net proceeds to the Company of approximately $195.8 million after deducting commissions and other transaction costs. Of those shares sold, 738,900 were sold in 2022, and 497,043 were sold in 2021. All shares were sold pursuant to the Company's effective shelf registration statement and the prospectus supplement relating thereto. As of December 31, 2022, no amounts remained reserved and available for sale under the 2021 Sales Agreement and the related prospectus supplement.

8. Stock-based Compensation

The 2015 Stock Plan, as amended, is our primary plan through which equity based grants are awarded. We ceased making new awards under the 2006 Stock Plan upon adoption of the 2015 Stock Plan. The 2015 Stock Plan provides for the grant of incentive stock options, non-statutory stock options, restricted stock and other stock-based compensation awards to employees, officers, directors, and consultants of the Company. The administration of the 2015 Stock Plan is under the general supervision of the Compensation Committee of the Board of Directors. The terms of stock options awarded under the 2015 Stock Plan, in general, are determined by the Compensation Committee, provided the exercise price per share generally shall not be set at less than the fair market value of a share of the common stock on the date of grant and the term shall not be greater than ten years from the date the option is granted. As of December 31, 2022, the Company had options outstanding to purchase 2,857,054 shares of its common stock. As of December 31, 2022, 890,029 shares were available for future issuance.

The following table summarizes stock option activity during the twelve months ended December 31, 2022:

	Shares	Weighted average exercise price	Weighted average remaining contractual life (years)	Aggregate intrinsic value (in thousands)
Outstanding at January 1, 2022	2,301,574	$ 78.90		
Options granted	860,795	81.39		
Options exercised	(215,784)	41.50		
Options cancelled	(89,531)	100.71		
Outstanding at December 31, 2022	2,857,054	$ 81.78	6.49	$ 596,279
Exercisable at December 31, 2022	1,610,185	$ 76.31	4.90	$ 345,162

The total cash received by the Company as a result of stock option exercises was $9.0 million, $1.0 million and $0.7 million for the years ended December 31, 2022, 2021, and 2020. The total intrinsic value of options exercised was $47.3 million $0.1 million and $4.1 million for the years ended December 31, 2022, 2021, and 2020. The weighted-average grant date fair values, based on the Black-Scholes option model, of options granted during the year ended December 31, 2022, 2021 and 2020 was $54.68, $73.29, and $68.07, respectively.

Stock-Based Compensation Expense

Stock-based compensation expense during the years ended December 31, 2022, 2021 and 2020 was as follows (in thousands):

	Year Ended December 31,		
	2022	2021	2020
Stock-based compensation expense by type of award:			
Stock options	$31,625	$26,873	$20,730
Total stock-based compensation expense	$31,625	$26,873	$20,730
Effect of stock-based compensation expense by line item:			
Research and development	$13,876	$10,698	$ 8,833
General and administrative	17,749	16,175	11,897
Total stock-based compensation expense included in net loss	$31,625	$26,873	$20,730

Unrecognized stock-based compensation expense on stock options as of December 31, 2022 was $58.7 million with a weighted average remaining period of 2.57 years.

9. Leases

In 2019, the Company entered into an operating lease for office space, which was renewed and extended in 2020. We adopted ASU 2016-02, “Leases,” on January 1, 2019 requiring, among other changes, operating and finance leases with terms exceeding twelve months to be recognized as a right-of-use asset (or “ROU”) and lease liabilities on the balance sheet. Operating lease ROU assets and operating lease liabilities are recognized based on the present value of the future minimum lease payments over the lease term at the commencement date. The lease term is determined to be the non-cancelable period including any lessee renewal options that are considered reasonably certain of exercise. The interest rate implicit in lease contracts is typically not readily determinable. As such, the Company used judgment to determine an appropriate incremental borrowing rate, which is the rate incurred to borrow on a collateralized basis over a similar term in a similar economic environment.

Future minimum payments under the Company’s operating leases related to the ROU asset and lease liability as of December 31, 2022 was as follows (in thousand):

	Operating Leases
2023	622
Thereafter	—
Total minimum payments	$ 622
Less: imputed interest	(20)
Present value of lease liabilities	$ 602

As of December 31, 2022, the weighted average remaining operating lease term was 0.7 years and the weighted average discount rate used to determine the operating lease liabilities was 6.72%. Cash paid related to

the lease liability was $0.7 and $0.4 million for years ended December 31, 2022 and 2021 respectively. Operating lease costs were $0.8 and $0.4 million for years ended December 31, 2022 and 2021 respectively. Rent, short term and variable leases costs were immaterial during the years ended December 31, 2022, 2021 and 2020.

10. Commitments and Contingencies

The Company has a Research, Development and Commercialization Agreement with Hoffmann-La Roche ("Roche") which grants the Company a sole and exclusive license to develop, use, sell, offer for sale and import any Licensed Product as defined by the agreement.

The agreement requires future milestone payments to Roche. In 2019, the Company commenced a Phase 3 study in Non-Alcoholic Steatohepatitis (NASH), which triggered a $2 million milestone payment under the agreement. Remaining milestones under the agreement total $8 million and are earned by achieving specified objectives related to future regulatory approval in the United States and Europe of a product developed from resmetirom. A single-digit royalty payment range is based on net sales of products developed from resmetirom, subject to certain reductions. Except as described above, the Company has not achieved any additional product development or regulatory milestones and had no Licensed Product sales for the years ended December 31, 2022, 2021 and 2020.

The Company has entered into customary contractual arrangements and letters of intent in preparation for and in support of the clinical trials.

11. Income Taxes

At December 31, 2022, the Company had federal net operating loss ("NOL") carryforwards of approximately $275.5 million available to reduce future taxable income, of which $40.4 million will expire between 2031 and 2037. The Company also has state operating loss carryforwards of approximately $264.2 million, available to reduce future taxable income, which expire between 2031 and 2041. The Company has unused federal research and development carryforwards of approximately $33.1 million which will begin to expire in 2031.

The Internal Revenue Code ("IRC") limits the amounts of NOL carryforwards that a Company may use in any one year in the event of certain cumulative changes in ownership over a three-year period as described in Section 382 of the IRC. Such change in ownership could limit the Company's utilization of the NOL, and could be triggered by subsequent sales of securities by the Company or stockholders. The deferred tax asset related to the NOL reflected on the financial statements could be affected by this limitation. Although a formal analysis has not been completed, the Company has determined that an ownership change likely occurred for Madrigal during the year ended December 31, 2017.

In assessing the realizability of deferred tax assets, management considers whether it is more likely than not that some portion of the deferred tax assets will not be realized. The ultimate realization of deferred tax assets is dependent upon the generation of future taxable income during the periods in which those temporary differences become deductible. As there is no assurance of future taxable income, a full valuation allowance has been established to offset the deferred tax assets. The valuation allowance increased $59.5 million for the year ended December 31, 2022. Changes in the deferred tax asset will be recorded as an income tax benefit or expense on the accompanying consolidated statements of operations.

Entities are also required to evaluate, measure, recognize and disclose any uncertain income tax provisions taken on their income tax returns. The Company has analyzed its tax positions and has concluded that as of December 31, 2022 there were no uncertain positions. The 2018 through 2022 tax returns are open to review by the IRS and state taxing authorities. Interest and penalties, if any, as they relate to income taxes assessed, are included in the income tax provision. There was no income tax related interest and penalties included in the income tax provision for 2022.

Temporary differences that give rise to deferred tax assets and liabilities are as follows (in thousands):

	For the years ended December 31,		
	2022	2021	2020
Deferred Tax Liabilities			
Unrealized gains on investments	$ —	$ —	$ 14
Total Deferred Tax Liabilities	$ —	$ —	$ 14
Deferred Tax Assets			
Charitable contributions	$ 45	$ 53	$ 51
Accrued expenses	2,398	1,857	1,318
Intangibles	589	783	883
Stock compensation	27,226	24,335	16,812
Property, plant & equipment	106	80	68
Unrealized loss on investment	8	23	—
Net operating losses	68,305	47,864	27,933
Capitalized R&D	137,328	112,848	71,128
R&D credit	35,103	23,799	14,205
Total deferred tax assets before valuation allowance	271,108	211,642	132,398
Valuation allowance	(271,108)	(211,642)	(132,384)
Total deferred tax assets	—	—	14
Net deferred tax assets	$ —	$ —	$ —

Differences between the effective income tax rate and the US statutory rate were as follows (in thousands):

	For the years ended December 31,		
	2022	2021	2020
Tax benefit at U.S. federal statutory rate	$ (62,023)	$ (50,788)	$ (17,629)
Stock based compensation	(7,844)	—	(47)
162M limitation	7,996	22	—
Other nondeductible expenses	16	5	14
State income taxes benefit before valuation allowance, net of federal benefit	13,090	(19,622)	(6,613)
Increase in domestic valuation allowance	59,466	79,258	26,843
Research and development credit	(10,712)	(9,002)	(2,636)
Other adjustments	11	127	68
Income tax expense (benefit)	$ —	$ —	$ —

12. Quarterly Financial Data (unaudited)

The following tables present a summary of quarterly results of operations for 2022 and 2021 (in thousands, except shares and per share data):

	Three months ended			
	March 31, 2022	June 30, 2022	September 30, 2022	December 31, 2022
Revenues:				
Total revenues	$ —	$ —	$ —	$ —
Operating expenses:				
Research and development	47,929	58,499	68,271	70,742
General and administrative	9,658	11,774	12,141	14,557
Total operating expenses	57,587	70,273	80,412	85,299
Loss from operations	(57,587)	(70,273)	(80,412)	(85,299)
Interest income	69	323	717	1,076
Interest expense	—	(780)	(1,502)	(1,682)
Other income	—	—	—	—
Net loss	$ (57,518)	$ (70,730)	$ (81,197)	$ (85,905)
Net loss per common share:				
Basic and diluted net loss per common share	$ (3.36)	$ (4.14)	$ (4.75)	$ (4.98)
Basic and diluted weighted average number of common shares outstanding	17,103,395	17,103,395	17,103,395	17,237,517

	Three months ended			
	March 31, 2021	June 30, 2021	September 30, 2021	December 31, 2021
Revenues:				
Total revenues	$ —	$ —	$ —	$ —
Operating expenses:				
Research and development	45,770	51,632	54,873	52,889
General and administrative	7,209	10,110	8,287	11,712
Total operating expenses	52,979	61,742	63,160	64,601
Loss from operations	(52,979)	(61,742)	(63,160)	(64,601)
Interest income	160	91	60	52
Interest expense	—	—	—	—
Other income	273	—	—	—
Net loss	$ (52,546)	$ (61,651)	$ (63,100)	$ (64,549)
Net loss per common share:				
Basic and diluted net loss per common share	$ (3.32)	$ (3.72)	$ (3.79)	$ (3.78)
Basic and diluted weighted average number of common shares outstanding	15,840,401	16,571,322	16,639,776	17,074,543

13. Subsequent Event

On February 3, 2023, the Company entered into the First Amendment (the "Amendment") to the Loan Facility described in Footnote 6 (as amended, the "Amended Loan Facility"). Under the terms of the Loan

Facility, the first $50.0 million tranche was drawn at closing in May 2022. Under the Amended Loan Facility, an additional $35.0 million was drawn under a second, expanded, $65.0 million tranche ("Tranche 2") in February of 2023 following the Company's achievement of the Phase 3 clinical development milestone. The Company has the ability to draw an additional $15.0 million under Tranche 2 by June 19, 2023 and an additional $15.0 million under Tranche 2 by September 30, 2023 (for a total of $30.0 million in additional committed Tranche 2 capacity). The third tranche ("Tranche 3") of $75.0 million remains unchanged by the Amendment, and such borrowings are available subject to the Company obtaining a certain FDA approval for resmetirom. Coincident with the expansion of Tranche 2 borrowing capacity by $15 million, the Amendment reduced the fourth tranche under the Loan Facility ("Tranche 4") by $15.0 million to $60.0 million , which amount is available subject to Hercules' sole discretion. In connection with the $35.0 million drawn under the second tranche at the closing of the Amendment, the Company issued to Hercules and affiliates Tranche 2 Warrants to purchase 2,453 shares of common stock at an exercise price of $285.31 per share. The Amendment reduced the interest rate under the Amended Loan Facility to the greater of (i) the prime rate as reported in The Wall Street Journal plus 2.45% and (ii) 8.25%. The Amendment and the Amended Loan Facility summary terms were disclosed in the Company's Current Report on Form 8-K filed with the Securities and Exchange Commission on February 9, 2023.

DESCRIPTION OF SECURITIES OF THE REGISTRANT

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, our Certificate of Designation of Preferences, Rights and Limitations of Series A Convertible Preferred Stock and our Certificate of Designation of Preferences, Rights and Limitations of Series B Convertible Preferred Stock. Our common stock is the only class of our securities registered under Section 12 of the Securities Exchange Act of 1934, as amended, and is listed on The Nasdaq Stock Market LLC. 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.

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

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 Select 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 December 31, 2022, we had (i) 1,969,797 shares of preferred stock, designated Series A Convertible Preferred Stock, outstanding held by two stockholders of record, and (ii) 400,000 shares of preferred stock, designated Series B 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, our Certificate of Designation of Preferences, Rights and Limitations of Series A Convertible Preferred Stock and our Certificate of Designation of Preferences, Rights and Limitations of Series B 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. A holder of Series A Convertible Preferred Stock, 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 (the "Exchange Act"), 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 and the holders of our Series B Convertible Preferred 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 pari passu with the shares of the Series B Convertible Preferred Stock, and 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.

Series B Convertible Preferred Stock

Each share of the Series B 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 as provided in the Certificate of Designation of Preferences, Rights and Limitations of Series B Convertible Preferred Stock. A holder of Series B Convertible Preferred Stock, however, will be prohibited from converting shares of the Series B 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 Exchange Act, which may be increased or decreased up to 19.99% 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 B Convertible Preferred Stock upon liquidation, the holders of the Series B Convertible Preferred Stock shall participate pari passu with the holders of our common stock and the holders of the Series A Convertible Preferred Stock (on an as-if-converted-to-common-stock basis) in our net assets. Shares of the Series B Convertible Preferred Stock will generally have no voting rights, except as required by law. Shares of the Series B Convertible Preferred Stock will be entitled to receive dividends pari passu with the shares of the Series A Convertible Preferred

Stock, and before shares of any other class or series of capital stock of the Company (other than dividends in the form of the 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) also is 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 662/3% 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.

MADRIGAL PHARMACEUTICALS, INC.
AMENDED 2015 STOCK PLAN
RESTRICTED STOCK UNIT AWARD
GRANT NOTICE

1. Name of Participant: _____

2. Grant Date of the RSUs (the "Grant Date"): _____

3. Number of RSUs: _____

4. **Vesting of Award:** Subject to the Participant's continuous employment or other service relationship with or to the Company or any of its Affiliates as an Employee, director, and/or Consultant from the Grant Date through each of the following applicable dates (each such date, a "**Vesting Date**"), the RSUs shall vest twenty-five percent (25%) of the Number of RSUs above on each of the first, second, third, and fourth anniversaries of the Grant Date. Any terms used and not defined herein have the meanings ascribed to such terms in the Madrigal Pharmaceuticals, Inc. Amended 2015 Stock Plan (as it has been and may be amended and/or restated from time to time, the "**Plan**").

By signing this Grant Notice or by electronic acknowledgment of this Grant Notice, the Participant acknowledges receipt of and agrees to all the terms and conditions described in this Restricted Stock Unit Award Grant Notice, the attached Restricted Stock Unit Agreement (including the Restrictive Covenants Agreement attached thereto), and the Plan. The Participant acknowledges that he or she has carefully reviewed the Plan and agrees that the Plan will control in the event any provision of the Agreement should appear to be inconsistent with the Plan.

MADRIGAL PHARMACEUTICALS, INC.

By: _____
Name: _____
Title: _____

_____
PARTICIPANT

ATTACHMENT: Restricted Stock Unit Agreement & Restrictive Covenants Agreement

MADRIGAL PHARMACEUTICALS, INC.
AMENDED 2015 STOCK PLAN
RESTRICTED STOCK UNIT AGREEMENT

This RESTRICTED STOCK UNIT AGREEMENT (the "**Agreement**") is made as of the "Grant Date" set forth in the Restricted Stock Unit Award Grant Notice ("**Grant Notice**") between MADRIGAL PHARMACEUTICALS, INC. (the "**Company**"), a Delaware corporation, and the individual whose name appears on the Restricted Stock Unit Award Grant Notice (the "**Participant**").

WHEREAS, the Company has adopted the Madrigal Pharmaceuticals, Inc. Amended 2015 Stock Plan (as it has been and may be amended and/or restated from time to time, the "**Plan**") to promote the interests of the Company by providing an incentive for Employees, directors, and Consultants of the Company and its Affiliates;

WHEREAS, pursuant to the provisions of the Plan, and in consideration for the Participant's past and future services to the Company and for compliance with certain Restrictive Covenants Agreement (as defined below) restrictions set forth herein, the Company desires to grant to the Participant restricted stock units ("**RSUs**") related to the Company's common stock, $0.0001 par value per share ("**Common Stock**"), in accordance with the provisions of the Plan, all on the terms and conditions hereinafter set forth; and

WHEREAS, the Company and the Participant understand and agree that any terms used and not defined herein have the meanings ascribed to such terms in the Plan.

NOW, THEREFORE, in consideration of the promises and the mutual covenants contained herein and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties hereto hereby agree as follows:

1. Grant of Award. The Company hereby grants to the Participant a Stock-Based Award for the number of RSUs set forth in the Grant Notice (the "**Award**"). Each RSU represents a contingent entitlement of the Participant to receive one share of Common Stock, on the terms and conditions and subject to all the limitations set forth herein, in the Grant Notice, and in the Plan, which are incorporated herein by reference.

2. Vesting of Award.

   a. Subject to the terms and conditions set forth in this Agreement and the Plan: (i) the Award shall vest as set forth in the Grant Notice and is subject to the other terms and conditions of this Agreement and the Plan; and (ii) upon vesting, the Participant shall be entitled to receive such number of shares of Common Stock equivalent to the number of such vested RSUs.

b. Notwithstanding anything to the contrary in the Grant Notice or this Agreement, any fractional Shares resulting from the vesting schedule set forth in the Grant Notice will be rounded to the nearest whole Share and shall be rounded up or down as necessary as of the last Vesting Date; provided, in all cases, the Participant cannot vest in more than the number of RSUs set forth in the Grant Notice.

3. Forfeiture of Unvested RSUs.

a. Except as otherwise set forth in this Agreement, the Grant Notice, the Plan, or a separate agreement between Participant and the Company, if the Participant ceases his or her continuous employment or other service relationship with or to the Company or any of its Affiliates as an Employee, director, and/or Consultant ("**Termination**"), then all then-unvested RSUs shall automatically and immediately be forfeited to the Company as of such Termination, and this Agreement and the Grant Notice shall automatically and immediately terminate and be of no further force or effect.

b. For purposes of this Agreement, the Participant's continuous employment or other service relationship with or to the Company or any of its Affiliates as an Employee, director, and/or Consultant does not terminate when the Participant goes on a bona fide leave of absence that was approved by the Administrator in writing, if the terms of the leave provide for continued service crediting, or when continued service crediting is required by applicable law. The Participant's continuous employment or other service relationship with or to the Company or any of its Affiliates as an Employee, director, and/or Consultant terminates in any event when the approved leave ends unless the Participant immediately returns to active work. The Administrator may determine, in its discretion, which leaves count for this purpose and when the Participant's continuous employment or other service relationship with or to the Company or any of its Affiliates as an Employee, director, and/or Consultant terminates for all purposes under the Plan in accordance with the provisions of the Plan.

c. This Award is expressly granted as consideration for the Participant's agreement to comply with the Confidentiality and Inventions and Restrictive Covenants Agreement attached as Exhibit A hereto (the "**Restrictive Covenants Agreement**"). Therefore, notwithstanding anything to the contrary contained in this Agreement, in the event that the Participant materially breaches the terms of the Restrictive Covenants Agreement, all of the Unvested RSUs then held by the Participant and all Common Stock issued upon the vesting of RSUs that are outstanding and held by the Participant shall be forfeited to the Company immediately upon written notice by the Company. No other awards granted to the Participant under the Plan shall be subject to the forfeiture and repayment obligation set forth in this Section 3.c.

4. Delivery of Award; Evidence of Issuance. Delivery of the Shares represented by the Participant's vested RSUs shall be made as soon as practicable after the applicable Vesting Date and, in any event, by no later than sixty (60) days following each applicable Vesting Date. The issuance of the Shares represented by the Participant's vested RSUs shall be evidenced in such a manner as the Administrator, in its discretion, deems appropriate, including, without limitation, by (i) book-entry registration or (ii) issuance of one or more share certificates.

5. Prohibitions on Transfer and Sale. This Award (including any additional RSUs received by the Participant as a result of stock dividends, stock splits, or any other similar transaction affecting the Company's securities without receipt of consideration) shall not be transferable, without the prior approval of the Administrator, by the Participant, by the Participant, other than by will or by the laws of descent and distribution. Except as provided in the previous sentence, the Shares to be issued pursuant to this Agreement shall be issued, during the Participant's lifetime, only to the Participant (or, in the event of legal incapacity or incompetence, to the Participant's guardian or representative), and this Award shall not be assigned, pledged, or hypothecated in any way (whether by operation of law or otherwise) and shall not be subject to execution, attachment, or similar process. Any attempted transfer, assignment, pledge, hypothecation, or other disposition of this Award or of any rights granted hereunder contrary to the provisions of this Section 5, or the levy of any attachment or similar process upon this Award, shall be null and void.

6. Adjustments. The Plan contains provisions covering the treatment of RSUs and Shares in a number of contingencies, such as stock splits and Corporate Transactions. Provisions in the Plan for adjustment with respect to this Award and the related provisions with respect to successors to the business of the Company are hereby made applicable hereunder and are incorporated herein by reference.

7. Securities Law Compliance. The Participant specifically acknowledges and agrees that any sales of Shares shall be made in accordance with the requirements of the Securities Act. The Company currently has an effective registration statement on file with the United States Securities and Exchange Commission with respect to the Shares to be granted hereunder. Despite registration, applicable securities laws may restrict the ability of the Participant to sell his or her Shares, including due to the Participant's affiliation with the Company. The Company shall not be obligated to either issue the Shares or permit the resale of any Shares if such issuance or resale would violate any applicable securities law, rule, or regulation.

8. Rights as a Stockholder. The Participant shall have no rights as a stockholder, including voting and dividend rights, with respect to the RSUs subject to this Agreement, unless and until Shares represented by the Participant's vested RSUs have been issued to the Participant and either a certificate evidencing the Shares has been issued or an appropriate entry has been made on the Company's books. No adjustments to Shares represented by the Participant's vested RSUs shall be made for dividends, distributions, or other rights on or with respect to the Common Stock generally if the applicable record date for any such dividend, distribution, or right occurs before the Participant's certificate is issued or an appropriate book entry is made, except as otherwise described in the Plan.

9. Incorporation of the Plan; Clawback. The Participant specifically understands and agrees that the RSUs and the Shares to be issued under the Agreement will be issued to the Participant pursuant to the Plan, a copy of which Plan the Participant acknowledges he or she has received, has read, and understands and by which Plan he or she agrees to be bound. The provisions of the Plan are incorporated herein by reference. In addition, the RSUs (and any compensation paid or Shares issued pursuant to this Agreement) is subject to recoupment in accordance with The Sarbanes-Oxley Act, The Dodd-Frank Wall Street Reform and Consumer Protection Act and any implementing regulations thereunder, any clawback policy adopted by the Company, and any compensation recovery policy otherwise required by applicable law. No recovery of compensation under such a clawback policy will be an event giving rise to a right to resign for "good reason" or for a "constructive termination" (or similar terms) under any agreement between the Participant and the Company or any Affiliate.

10. Tax Liability of the Participant and Payment of Taxes. The Participant acknowledges and agrees that any income or other taxes due from the Participant with respect to this Award or the Shares to be issued pursuant to this Agreement or otherwise sold shall be the Participant's responsibility. In the event that the Company or an Affiliate determines that any federal, state, local, or foreign tax or withholding payment is required relating to the RSUs, or the delivery of Shares with respect to this Award, the Company or any Affiliate, subject to the proviso below, will have the right to withhold the delivery of vested Shares otherwise deliverable under this Agreement to meet such obligations, provided that, to the extent required to avoid adverse accounting consequences to the Company, the Shares so withheld will have an aggregate Fair Market Value not exceeding the minimum amount of tax required to be withheld by applicable laws and fractional Shares will not be retained to satisfy any portion of the Company's withholding obligation (such process, "**Net Settlement**"); provided, however, the Administrator shall have the discretion to override Net Settlement, (i) provided ninety (90) days' advance notice is given prior to a Vesting Date from the Company to the Participant, in which case such withholding shall be through a "same day sale" commitment with a broker-dealer that is a member of the Financial Industry Regulatory Authority (a "**FINRA Dealer**"), whereby the Participant irrevocably elects to sell a portion of the Shares to be delivered in connection with the RSUs to satisfy

withholding obligations and whereby the FINRA Dealer irrevocably commits to forward the proceeds necessary to satisfy the withholding obligations directly to the Company or any Affiliate ("**Sell to Cover**") or (ii)(A) in lieu of withholding (under Net Settlement) or selling (under Sell to Cover) a fractional vested Share or (B) in connection with withholding obligations arising outside the ordinary course, such as outside annual Vesting Dates of the RSUs, and in each case under (A) or (B) such withholding may be through deduction from payments of any kind otherwise due to the Participant.

The Participant hereby (i) agrees that the Company or any Affiliate shall be entitled to use the foregoing methods to recover such taxes and (ii) acknowledges that, absent further action by the Administrator, in the event that the Company or an Affiliate determines that any federal, state, local, or foreign tax or withholding payment is required relating to the RSUs, or the delivery of Shares with respect to this Award, the Company or any Affiliate will utilize Net Settlement.

The Participant further agrees that the Administrator may, as it reasonably considers necessary, amend or vary this Agreement due to changes in tax laws to facilitate such recovery of taxes.

11. Participant Acknowledgements and Authorizations. The Participant hereby acknowledges the following:

a. Neither the Company nor any Affiliate is, by the Plan or this Award, obligated to continue the Participant as an Employee, director, or Consultant of the Company or an Affiliate. Unless otherwise specified in a written employment or other written compensatory agreement between the Participant and the Company or an Affiliate, the Company or any Affiliate, as applicable, reserves the right to terminate the Participant's employment or other service relationship with the Company or an Affiliate at any time and for any reason.

b. The Plan is discretionary in nature and may be suspended or terminated by the Company at any time.

c. The grant of this Award is considered a one-time benefit and does not create a contractual or other right to receive any other award under the Plan, benefits in lieu of awards, or any other benefits in the future.

d. The Plan is a voluntary program of the Company and future awards, if any, will be at the sole discretion of the Company, including, but not limited to, the timing of any grant, the amount of any award, vesting provisions, and the purchase price, if any.

e. The value of this Award is an extraordinary item of compensation outside of the scope of the Participant's employment or consulting contract, agreement, or arrangement. As such, the Award is not part of normal or expected compensation for purposes of calculating any severance, resignation, redundancy, end of service payments, bonuses, long-service awards, pension or retirement benefits, or similar payments. The future value of the shares of Common Stock is unknown and cannot be predicted with certainty.

f. The Participant (i) authorizes the Company and each Affiliate and any agent of the Company or any Affiliate administering the Plan or providing Plan recordkeeping services to disclose to the Company or any of its Affiliates such information and data as the Company or any such Affiliate shall request in order to facilitate the grant of the Award and the administration of the Plan; and (ii) authorizes the Company and each Affiliate to store and transmit such information in electronic form for the purposes set forth in this Agreement.

g. The obligation of the Company to deliver Shares pursuant to this Award constitutes an unfunded and unsecured obligation of the Company. Until Shares are delivered, the Participant shall have no rights under this Agreement or the Plan, other than those of a general unsecured creditor of the Company. No assets of the Company shall be set aside for the settlement of the RSUs.

12. Notices. By accepting the Award, the Participant agrees that notices may be given to the Participant in writing either at the Participant's home or mailing address as shown in the records of the Company or an Affiliate or by electronic transmission (including e-mail or reference to a website or other URL) sent to the Participant through the normal process employed by the Company or the Affiliate, as applicable, for communicating electronically with its employees or other service providers.

13. Assignment and Successors.

a. This Agreement is personal to the Participant and, without the prior approval of the Administrator, shall not be assignable by the Participant, other than by will or the laws of descent and distribution. This Agreement shall inure to the benefit of and be enforceable by the Participant's legal representatives and beneficiaries.

b. This Agreement shall inure to the benefit of and be binding upon the Company and its successors and assigns.

14. Governing Law. This Agreement shall be construed and enforced in accordance with the laws of the State of Delaware, without giving effect to the conflict of law principles thereof; provided that, for the avoidance of doubt, the Restrictive Covenants Agreement shall continue to be governed solely by Pennsylvania law. For the purpose of litigating any dispute that arises under this Agreement, whether at law or in equity, the parties hereby consent to exclusive jurisdiction in the Commonwealth of Pennsylvania and agree that such litigation shall be conducted in the state courts of the Commonwealth of Pennsylvania or the federal courts of the United States for the Eastern District of Pennsylvania.

15. Severability. If any provision of this Agreement is held to be invalid or unenforceable by a court of competent jurisdiction, then such provision or provisions shall be modified to the extent necessary to make such provision valid and enforceable, and to the extent that this is impossible, then such provision shall be deemed to be excised from this Agreement, and the validity, legality, and enforceability of the rest of this Agreement shall not be affected thereby.

16. Entire Agreement. This Agreement, together with the Grant Notice, the Restrictive Covenants Agreement, and the Plan, constitutes the entire agreement and understanding between the parties hereto with respect to the subject matter hereof and supersedes all prior oral or written agreements and understandings relating to the subject matter hereof, including without limitation any offer letter provision related to the subject matter hereof. No statement, representation, warranty, covenant, or agreement not expressly set forth in this Agreement shall affect or be used to interpret, change, or restrict the express terms and provisions of this Agreement; provided, however, in any event, this Agreement shall be subject to and governed by the Plan.

17. Modifications and Amendments; Waivers and Consents. The terms and provisions of this Agreement may be modified or amended as provided in the Plan. Except as provided in the Plan, the terms and provisions of this Agreement may be waived, or consent for the departure therefrom granted, only by written document executed by the party entitled to the benefits of such terms or provisions. No such waiver or consent shall be deemed to be or shall constitute a waiver or consent with respect to any other terms or provisions of this Agreement, whether or not similar. Each such waiver or consent shall be effective only in the specific instance and for the purpose for which it was given, and shall not constitute a continuing waiver or consent.

18. Code Section 409A. The Award of RSUs evidenced by this Agreement is intended to be exempt from the nonqualified deferred compensation rules of Code Section 409A as a “short-term deferral” within the meaning of Code Section 409A and, to the maximum extent permitted, shall be construed accordingly. Notwithstanding anything to the contrary in the Plan or this Agreement, none of the Company, its Affiliates, the Board of Directors, the Administrator, or any of their respective agents or delegates will have any obligation to take any action to prevent the assessment of any excise tax or penalty on the Participant under Code Section 409A, and none of the Company, its Affiliates, the Board of Directors, the Administrator, or any of their respective agents or delegates will have any liability to the Participant or any other person for such tax or penalty.

To the extent that the RSUs constitute "deferred compensation" under Code Section 409A, a termination of Service occurs only upon an event that would be a "separation from service" within the meaning of Code Section 409A. If, at the time of the Participant's "separation from service," (i) the Participant is a "specified employee" within the meaning of Code Section 409A (and as applied according to procedures of the Company and its Affiliates), and (ii) the Administrator makes a good faith determination that an amount payable under this Agreement on account of the Participant's separation from service constitutes deferred compensation (within the meaning of Code Section 409A), the payment of which is required to be delayed pursuant to the six (6)-month delay rule set forth in Code Section 409A to avoid taxes or penalties under Code Section 409A (the "**Delay Period**"), then the Company will not pay such amount on the otherwise scheduled payment date but will instead pay it in a lump sum on the first business day after the Delay Period (or upon the Participant's death, if earlier), without interest. Each installment of RSUs that vest under this Agreement (if there is more than one installment) will be considered one of a series of separate payments for purposes of Code Section 409A.

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Exhibit A

Restrictive Covenants Agreement

Exhibit 21.1

SUBSIDIARIES OF MADRIGAL PHARMACEUTICALS, INC.

Madrigal Pharmaceuticals EU Limited, an Ireland company

Synta Limited Incorporated, a United Kingdom company

Canticle Pharmaceuticals, Inc., a Delaware corporation

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-3 (Nos. 333-256666 and 333-219304) and Form S-8 (Nos. 333-141903, 333-152824, 333-173862, 333-181117, 333-187243, 333-194477, 333-202680, 333-206128, 333-212615, 333-224503, 333-249866 and 333-257506) of Madrigal Pharmaceuticals, Inc. of our report dated February 24, 2022 relating to the financial statements and the effectiveness of internal control over financial reporting, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP

Philadelphia, Pennsylvania
February 23, 2023

Exhibit 31.1

CERTIFICATION OF PRINCIPAL EXECUTIVE OFFICER PURSUANT TO SECURITIES EXCHANGE ACT RULES 13A-14(a) AND 15D-14(a) AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Paul A. Friedman, M.D., certify that:

1. I have reviewed this Annual Report on Form 10-K of Madrigal Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

/s/ PAUL A. FRIEDMAN, M.D.

Paul A. Friedman, M.D.
Chief Executive Officer and Chairman of the Board
(Principal Executive Officer)
Date: February 23, 2023

Exhibit 31.2

CERTIFICATION OF PRINCIPAL FINANCIAL OFFICER PURSUANT TO SECURITIES EXCHANGE ACT RULES 13A-14(a) AND 15D-14(a) AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Alex G. Howarth, certify that:

1. I have reviewed this Annual Report on Form 10-K of Madrigal Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

/s/ ALEX G. HOWARTH

Alex G. Howarth
Chief Financial Officer (Principal Financial Officer)
Date: February 23, 2023

Exhibit 32.1

**CERTIFICATIONS PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO SECTION 906
OF THE SARBANES-OXLEY ACT OF 2002**

Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 (Subsections (a) and (b) of Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. Section 1350)), each of the undersigned officers of Madrigal Pharmaceuticals, Inc., a Delaware corporation (the "Company"), does hereby certify, to such officer's knowledge, that:

The Annual Report on Form 10-K for the fiscal year ended December 31, 2022 (the "Form 10-K") of the Company fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, and the information contained in the Form 10-K fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated February 23, 2023

/s/ PAUL A. FRIEDMAN, M.D.
Paul A. Friedman, M.D.
Chief Executive Officer and Chairman of the Board
(Principal Executive Officer)

Dated: February 23, 2023

/s/ ALEX G. HOWARTH
Alex G. Howarth
Chief Financial Officer (Principal Financial Officer)

A signed original of this written statement required by Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. Section 1350), has been provided to the Company and will be retained by the Company and furnished to the Securities and Exchange Commission or its staff upon request. These certifications accompany the Form 10-K, are not deemed filed with the Securities and Exchange Commission, and are not to be incorporated by reference into any filing of the Company under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.