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, 2023

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	
(Address of Principal Executive Offices)	**19428 (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, 2023 (the last business day of the registrant's most recently completed second fiscal quarter), as reported on the Nasdaq Global Market, was $3,158,123,661. For purposes of this calculation, beneficial ownership by directors and executive officers of the registrant has been excluded as they have been deemed affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

As of February 22, 2024, the registrant had 19,897,425 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 2024 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, Pennsyl

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K for the fiscal year ended December 31, 2023 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, 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 (consistent with fibrosis stages 2 and 3),
- 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, including all statements concerning potential clinical benefit to support accelerated approval and/or potential approval,
- Estimates of patients diagnosed with NASH,
- 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,
- The relationship between NASH progression and adverse patient outcomes,
- The estimated clinical burden of uncontrolled NASH,
- Analyses for patients with NASH with significant fibrosis concerning potential progression to cirrhosis, decompensated cirrhosis, liver transplant or death, and cardiovascular risks, comorbidities and outcomes,
- 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 significant fibrosis,
- Anticipated or estimated future results of operations and expenses, and our long-term liquidity expectations as we expand our resmetirom clinical development program and our commercial development program,
- Strategies, objectives and commercial opportunities, including potential prospects or results,
- 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 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,
- The potential impact of cyber attacks and other security incidents on our operations or business,
- 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; 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; our ability to prevent and/or mitigate cybersecurity attacks, unauthorized exfiltration of data or other security incidents; 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; and uncertainties concerning analyses or assessments outside of a controlled clinical trial. 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 FACTORS 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 incurred significant operating losses since inception. If we are unable to obtain regulatory approval for and successfully commercialize resmetirom, our business and stock price will be materially harmed.
- 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 approved, we will be highly dependent on the commercial success of resmetirom. We may not be able to meet expectations with respect to sales of our products if approved by the FDA, or attain profitability and positive cash-flow from operations. Furthermore, we operate in a highly competitive industry and our product may become obsolete.
- 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.
- If the FDA or other applicable regulatory authorities approve generic products that compete with any of our product candidates, the sales of our product candidates would be adversely affected.
- Resmetirom has only been studied in a limited number of patients. Following commercial launch, if approved, resmetirom will be available to a much larger number of patients, and we do not know whether the results of resmetirom's use in such larger number of patients will be consistent with the results from our clinical studies.
- The insurance coverage and reimbursement status of newly-approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for new or current products could limit our ability to market those products and decrease our ability to generate revenue.
- The pricing of pharmaceutical products has come under increasing scrutiny as part of a global trend toward healthcare cost containment. Resulting changes in healthcare law and policy, including recently enacted changes to Medicare, may impact our business in ways that we cannot currently predict.
- If any product liability lawsuits are successfully brought against us, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.
- 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.
- If the third parties on which we rely for the conduct of our clinical trials and manufacturing do not perform in accordance with good clinical practices and regulatory requirements, we may be unable to obtain regulatory approval for or commercialize our product candidates.
- A failure of our information technology infrastructure and cybersecurity threats may adversely affect our business and operations.
- If we lose key senior management personnel, it could have a material adverse effect on our business and stock price.

Risks Relating to Our Intellectual Property

- 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 able to protect our intellectual property rights throughout the world.

Risks Relating to Our Financial Position, Need for Capital and Existing Indebtedness

- 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 failure to comply with the covenants or other terms of the Loan and Security 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. In addition, any sale of shares into the market by our large stockholders, or the perception that sales could occur, in the future could cause the market price of our common stock to drop significantly.

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

We are a clinical-stage biopharmaceutical company pursuing novel therapeutics for nonalcoholic steatohepatitis, or NASH, a liver disease with high unmet medical need. Our lead candidate, resmetirom, is a once-daily, oral, liver-directed thyroid hormone receptor-β (THR-β) agonist designed to target key underlying causes of NASH.

NASH Disease State Overview. NASH is a more advanced form of nonalcoholic fatty liver disease (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. NASH is the leading cause of liver transplants in the U.S. for women, and is expected to soon be the leading cause of liver transplants overall. Additionally, patients with NASH, especially those with more advanced metabolic risk factors (hypertension, concomitant type 2 diabetes), are at increased risk for adverse cardiovascular events and increased morbidity and mortality. Once patients progress to NASH with significant fibrosis (consistent with fibrosis stages 2 and 3), the risk of adverse liver outcomes increases substantially.

NASH is also known as "metabolic dysfunction-associated steatohepatitis (MASH)" following a change in disease nomenclature introduced by hepatology medical societies in 2023.

Our Patient Focus. Madrigal estimates that approximately 1.5 million patients have been diagnosed with NASH in the U.S., of which approximately 525,000 have NASH with significant fibrosis. Madrigal estimates that approximately 315,000 diagnosed patients with NASH with significant fibrosis are under the care of the liver specialist physicians Madrigal will be targeting during the planned launch of resmetirom following approval.

Our Clinical Development Program. Madrigal is currently conducting multiple Phase 3 clinical trials to evaluate the safety and efficacy of resmetirom for the treatment of NASH, including the pivotal MAESTRO-NASH biopsy study in patients with significant fibrosis, the MAESTRO-NASH Outcomes study in patients with NASH with compensated cirrhosis and the MAESTRO-NAFLD-1 safety study. Positive results from the pivotal MAESTRO-NASH biopsy study were published in the *New England Journal of Medicine* in February 2024.

Data from the 52-week first 1,000 patient portion of MAESTRO-NASH, together with data from MAESTRO-NAFLD-1, the open-label extension of the MAESTRO-NAFLD-1 study, Phase 2 and Phase 1 data, including safety parameters, formed the basis for Madrigal's subpart H submission to the FDA for accelerated approval of resmetirom for treatment of NASH with liver fibrosis.

The following chart summarizes the status of our Phase 3 clinical development program for resmetirom:

Trial	**MAESTRO-NASH** Significant Fibrosis	**MAESTRO-NAFLD-1** Safety	**MAESTRO-NASH OUTCOMES** Compensated Cirrhosis
Study Design	Evaluates NASH resolution and/or fibrosis improvement on liver biopsy and composite clinical events	Evaluates safety & tolerability as measured by incidence of adverse events	Event-driven trial evaluating progression to hepatic decompensation
Study Duration	52 weeks biopsy (completed); 54 months clinical outcomes	52 weeks (completed)	~36 months
Patient Enrollment	~1,750 patients (ongoing)	~1,200 patients, including 200 with compensated cirrhosis	~700 patients (recruiting)

Key Developments

In February 2024, primary results from the MAESTRO-NASH study were published in the *New England Journal of Medicine.*

In September 2023, Madrigal announced we had commenced a public underwritten offering of common stock and pre-funded warrants to purchase common stock (the "Offering"). The Offering closed in October 2023. We received gross proceeds totaling $500.0 million. Our net proceeds were $472.0 million, after deducting fees and commissions. We intend to use the net proceeds from the Offering for our clinical and commercial activities in preparation for a potential launch of resmetirom in the U.S. and for general corporate purposes, including, without limitation, research and development expenditures, clinical trial expenditures, manufacture and supply of drug substance and drug products, potential acquisitions or licensing of new technologies, capital expenditures and working capital.

Also in September 2023, Madrigal announced our Board of Directors (the "Board") appointed Bill Sibold as the President and Chief Executive Officer of the Company. In connection with this appointment, the size of the Board was increased to nine, and Mr. Sibold was also appointed a member of the Board. On Mr. Sibold's start date, he assumed the duties and responsibilities of the Company's principal executive officer from Paul Friedman, M.D., who previously served as the Chief Executive Officer since July of 2016. Dr. Friedman continues to serve on the Board as a director of the Company.

Additionally in September 2023, the U.S. Food and Drug Administration (the "FDA") informed Madrigal that it accepted for review our New Drug Application ("NDA") for resmetirom for the treatment of adult patients with NASH with liver fibrosis and granted a Priority Review designation. The FDA assigned a Prescription Drug User Fee Act ("PDUFA") date of March 14, 2024, the target date by which the FDA intends to complete its review and take action on the NDA. The FDA noted in its September 2023 correspondence that it was not currently planning to hold an advisory committee meeting to discuss our application.

In April 2023, Madrigal announced that resmetirom received Breakthrough Therapy designation from the FDA for the treatment of patients with NASH with liver fibrosis. Breakthrough Therapy designation is a process intended to expedite the development and review of drugs for serious or life-threatening conditions. The criteria for breakthrough therapy designation require preliminary clinical evidence that demonstrates the drug may have substantial improvement on at least one clinically significant endpoint over available therapy, or over placebo if there is no available therapy. A drug that receives Breakthrough Therapy designation is eligible for more intensive guidance on an efficient drug development program and organizational commitment involving senior managers from FDA.

Also in April 2023, Madrigal announced that the outcomes portion of the Phase 3 MAESTRO-NASH biopsy trial completed enrollment. Enrollment of the MAESTRO-NASH study was closed at approximately 1,750 patients based on the enrollment target of the 54-month long-term clinical outcome portion of the study.

Clinical Trial Overview

MAESTRO-NASH TRIAL. In December 2022, Madrigal announced topline results from the pivotal Phase 3 MAESTRO-NASH biopsy study of resmetirom and the primary results were published in the *New England Journal of Medicine* in February 2024. 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 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 significant 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 0, inflammation 0,1 with ≥2-point reduction in NAS) and no worsening of fibrosis	25.9	<0.001	29.9	<0.001	
≥1-stage improvement in fibrosis with no worsening of NAS	24.2	<0.001	25.9	<0.001	
Key Secondary Endpoint					
LDL-C lowering (24 weeks)	-13.6	<0.001	-16.3	<0.001	

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.

Safety

The frequency of serious adverse events (SAEs) was similar across treatment arms in the MAESTRO-NASH trial: 11%, 13% and 12% for the 80 mg, 100 mg, and placebo groups, respectively. The rate of study discontinuation for adverse events over the entire treatment period was low: 2.8%, 7.7% and 3.4 % 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 27%, 33%, 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. Approximately 50% of the diarrhea AEs were described as "worsening of preexisting diarrhea" or "intermittent/loose stool(s)"; no episodes of severe diarrhea were reported. The median duration of diarrhea was approximately 15-20 days, independent of resmetirom dose.

Study data indicated resmetirom treatment had no effect on heart rate or body weight and was not associated with arrhythmias. Blood pressure appeared slightly reduced among resmetirom-treated patients. Sex hormones were unchanged from baseline. Independent of thyroxine replacement status, resmetirom treatment reduced prohormone T4, as reflected by free thyroxine (FT4), by approximately 16-19% with no effect on thyroid-stimulating hormone (TSH) or the active thyroid hormone, free triiodothyronine (FT3). Relative to placebo resmetirom treated patients did not show increases in fractures, or fracture risk scores.

MAESTRO-NASH Safety Summary (Primary Population)

no. (%)	Resmetirom 80 mg (n = 322)	Resmetirom 100 mg (n = 323)	Placebo (n = 321)
≥1 AE	296 (91.9)	296 (91.6)	298 (92.8)
Grade 1 (mild)	73 (22.7)	66 (20.4)	77 (24.0)
Grade 2 (moderate)	180 (55.9)	183 (56.7)	169 (52.6)
≥Grade 3 (severe)	43 (13.4)	47 (14.6)	52 (16.2)
≥1 drug-related AEs	124 (38.5)	134 (41.5)	88 (27.4)
≥1 serious AE	35 (10.9)	41 (12.7)	37 (11.5)
≥1 drug-related serious AE	2 (0.6)	0	1 (0.3)
TEAEs leading to study discontinuation prior to Week 52	6 (1.9)	22 (6.8)	7 (2.2)
TEAEs leading to study discontinuation (entire treatment period)	9 (2.8)	25 (7.7)	11 (3.4)
Fatal AE*	1 (0.3)	2 (0.6)	1 (0.3)
3-pt MACE** (adjudicated)	1 (0.3)	1 (0.3)	1 (0.3)
Other cardiovascular event (adjudicated)	0	1 (0.3)	3 (0.9)
Common AEs (>10%)			
Diarrhea	87 (27.0)	108 (33.4)	50 (15.6)
COVID-19	69 (21.4)	54 (16.7)	66 (20.6)
Nausea	71 (22.0)	61 (18.9)	40 (12.5)
Arthralgia	48 (14.9)	35 (10.8)	40 (12.5)
Back pain	35 (10.9)	27 (8.4)	38 (11.8)
Urinary tract infection	33 (10.2)	27 (8.4)	27 (8.4)
Fatigue	33 (10.3)	26 (8.0)	28 (8.7)
Pruritus	26 (8.1)	37 (11.5)	22 (6.9)

*None of the fatal AEs in the table were treatment-related AEs.
**Nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death.

AE, adverse event; GI, gastrointestinal; MACE, major adverse cardiovascular event; TEAE, treatment emergent adverse event.

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. The MAESTRO-NAFLD-1 study was published in *Nature Medicine* in November 2023. 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 (
ApoB %CFB (SE) (Week 24)	-22 (1.5)	-14.6 (1.5)	<.0001	-16.6 (1.6)	<.0001	-0.1 (
MRI-PDFF %CFB (Week 16)	-49 %	-41 %	<.0001	-48 %	<.0001	-
Liver volume PDFF correction %CFB	-60 %					
MRI-PDFF %CFB (Week 52)	-53 %	-43 %	<.0001	-48 %	<.0001	-
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 (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

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

MAESTRO-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 compensated NASH cirrhosis.

RESMETIROM PHASE 2 CLINICAL TRIAL in NASH. 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 2019.

Lead Product Candidate—Resmetirom

Resmetirom is a once-daily, oral, liver-directed THR-β agonist designed to target key underlying causes of NASH. 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-ß agonists in tissues such as heart and bone.

Resmetirom is the only investigational medication for the treatment of NASH that has achieved two primary endpoints that FDA proposed as reasonably likely to predict clinical benefit in a Phase 3 trial: NASH resolution with no worsening of fibrosis and fibrosis reduction with no worsening of NAFLD activity score (NAS).

Our Strategy

Our goal is to become a leading biopharmaceutical company developing and commercializing innovative medications for the treatment of NASH. To achieve our goal, we plan to:

- ***Obtain regulatory approval of resmetirom in NASH.*** The resmetirom pivotal Phase 3 trial is the only Phase 3 trial in NASH to achieve both primary endpoints that FDA proposed as reasonably likely to predict clinical benefit: NASH resolution with no worsening of fibrosis and fibrosis reduction with no worsening of NAFLD activity score. Resmetirom received Breakthrough Therapy designation from the FDA and is under review to become the first medicine approved to treat patients with NASH with liver fibrosis. The FDA granted resmetirom Priority Review and assigned a Prescription Drug User Fee Act (PDUFA) date of March 14, 2024, the target date by which FDA intends to complete its review.
- ***Deliver on the U.S. launch of the first-to-market medicine for NASH.*** We intend to launch resmetirom in the U.S. for patients who have NASH with significant fibrosis (consistent with fibrosis stages 2 and 3). To support the launch, we have established a full capability commercial organization including marketing, sales and market access expertise. Patients with NASH with significant fibrosis are primarily managed by a concentrated group of NASH specialists in the United States. We believe this will enable us to execute on a specialty launch of resmetirom in an efficient, targeted manner. Resmetirom's product profile as a liver-directed, once-daily, oral therapy, as well as its first-to-market position, provide meaningful points of differentiation in the NASH competitive landscape.

- ***Expand our commitment to NASH.*** We intend to maximize the full value of resmetirom by broadening its indication. We are conducting a Phase 3 outcomes trial in patients with compensated cirrhosis. A positive outcome is expected to support the full approval of resmetirom for noncirrhotic NASH and an additional indication for resmetirom in patients with compensated NASH cirrhosis. We believe this outcomes data would be generated in advance of future competitors. In addition, we are evaluating the opportunity for resmetirom outside of the U.S. Furthermore, we expect to build on resmetirom's strong foundation through internal as well as external efforts, including accessing external innovation.

Target Indications

Nonalcoholic Steatohepatitis

Overview and Market Opportunity

NASH is a is a more advanced form of nonalcoholic fatty liver disease (NAFLD). Reported estimates state that 3-5% of adults have NASH, but the substantial majority of patients are undiagnosed. NASH is a leading cause of liver-related mortality and an increasing burden on healthcare systems globally. Additionally, patients with NASH, especially those with more advanced metabolic risk factors (hypertension, concomitant type 2 diabetes), are at increased risk for adverse cardiovascular events and increased morbidity and mortality. Once patients progress to NASH with significant fibrosis (consistent with fibrosis stages 2 and 3), the risk of adverse liver outcomes increases dramatically. NASH is rapidly becoming the leading cause of liver transplantation in the U.S.

Madrigal estimates that approximately 1.5 million patients have been diagnosed with NASH in the U.S., of which approximately 525,000 have NASH with significant fibrosis. Madrigal estimates that approximately 315,000 diagnosed patients with NASH with significant fibrosis are under the care of the liver specialist physicians Madrigal will be targeting during the planned launch of resmetirom following approval.

Other NASH Disease State Characteristics

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. 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.

NASH is the leading cause of liver transplants for women in the U.S. and is expected to soon be the leading cause of liver transplants overall. 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 approved treatments for NASH.

Resmetirom Commercial Strategy

We intend to launch resmetirom as a specialty medication for patients with NASH with significant fibrosis (consistent with fibrosis stages 2 and 3) treated by liver specialist physicians.

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, Madrigal estimates that approximately 1.5 million patients have been diagnosed with NASH in the U.S., of which approximately 525,000 have NASH with significant fibrosis. Madrigal estimates that approximately 315,000 diagnosed patients with NASH with significant fibrosis are under the care of the liver specialist physicians Madrigal will be targeting during the planned launch of resmetirom following approval. Over time, as disease awareness improves and disease prevalence increases, we expect the number of identified NASH patients with significant fibrosis eligible for treatment could grow.

Madrigal's launch plan for resmetirom includes a focus on educating physicians about the role of noninvasive tests for identifying patients who may be appropriate for resmetirom treatment, which have been reflected in published guidance documents from multiple medical societies.

To evaluate the potential value and cost effectiveness of resmetirom as a treatment for NASH patients with significant fibrosis, we 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 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 engaged in the assessment process by responding to data requests from ICER and providing public comment on ICER's cost-effectiveness modeling methods. In May 2023, a "Final Evidence Report" was released with ICER's 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. ICER analyses suggested resmetirom would achieve common thresholds for cost-effectiveness if priced between $39,600 – $50,100 per year assuming that short-term effects on liver fibrosis translate into longer-term reductions in cirrhosis. The cost-effectiveness threshold analyses included in ICER's Final 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.

Our commercial strategy in the U.S. includes a focus on access to therapy. We will distribute resmetirom through a specialty pharmacy network and, to support patient access and affordability, we will provide patient support services including reimbursement programs and educational support to help appropriate 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 potential launch of resmetirom that focuses on educating approximately 14,000 NASH specialist healthcare providers (hepatologists, gastroenterologists, a small number of endocrinologists and the associated advanced practice providers) in clinics that already treat NASH patients with significant fibrosis. Patient marketing initiatives include unbranded NASH disease education resources prior to potential approval of resmetirom, which will be followed by branded product advertising post-approval.

We intend to commercialize resmetirom alone in the U.S. and are evaluating strategic options for commercializing resmetirom in ex-U.S. territories.

Resmetirom in NASH Clinical Development Program

Our Clinical Development Program. Madrigal is currently conducting multiple Phase 3 clinical trials to evaluate the safety and efficacy of resmetirom for the treatment of NASH:

- The pivotal MAESTRO-NASH (Significant Fibrosis) study includes a 52-week biopsy assessment to support accelerated approval and an ongoing 54-month outcomes study designed to generate confirmatory data that, if positive, will help verify resmetirom's clinical benefit and support full approval. Positive topline results from the study were reported in December 2022 the primary results were published in the *New England Journal of Medicine* in February 2024.

- MAESTRO-NASH Outcomes (Compensated Cirrhosis) evaluates progression to liver decompensation events in patients with compensated NASH cirrhosis treated with resmetirom versus placebo. A positive outcome is expected to support the full approval of resmetirom for noncirrhotic NASH and expand the eligible patient population for resmetirom with an additional indication in patients with compensated NASH cirrhosis.
- The MAESTRO-NAFLD-1 (Safety) study was designed to noninvasively evaluate the safety and tolerability of resmetirom and provide a larger safety database to support regulatory benefit-risk assessment. Positive topline results from the study were reported in January 2022 and the primary publication appeared in *Nature Medicine*. MAESTRO-NAFLD-OLE, an open-label active treatment extension of MAESTRO-NAFLD-1, is ongoing to collect additional safety data in patients with noncirrhotic NASH and patients with compensated NASH cirrhosis.

The Company completed a Phase 2 clinical trial in NASH in 2018. This clinical trial was published in the *Lancet*.

Data from the 52-week first 1,000 patient portion of MAESTRO-NASH, together with data from MAESTRO-NAFLD-1, MAESTRO-NAFLD-OLE, Phase 2 and Phase 1 data, including safety parameters, formed the basis for Madrigal's subpart H submission to FDA for accelerated approval of resmetirom for treatment of NASH with liver fibrosis.

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 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 $2.0 million related milestone payment. The remaining milestone payment obligations under the Roche Agreement total $8.0 million, of which $5.0 million is tied to regulatory approval in the United States and $3.0 million is tied to regulatory approval in a major market country in Europe, in each case for resmetirom or any derivative product. Except as described above, we have not achieved any additional product development or regulatory milestones under the Roche Agreement and, as of the filing date of this Form 10-K, 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 not to pursue the development or commercialization of resmetirom in certain jurisdictions, 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 include companies with substantially greater financial, technical, and personnel resources than us. In addition, our competitors may 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;
- 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 numerous drugs in development for the treatment of NASH by companies ranging in size from pre-public biotech companies to large pharma organizations that have product candidates in clinical development for the treatment of NASH. While no company has reported positive topline Phase 3 data like Madrigal, we are aware of several companies with investigational NASH medications in active Phase 3 testing, including Novo Nordisk, Inventiva and Akero.

Glucagon-like peptide 1 (GLP-1) agonists and dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) agonists are being studied for the treatment of NASH in Phase 2 and Phase 3 trials. As of the date of this filing, there have been no successful Phase 3 trials evaluating a GLP-1 agonist or dual GLP-1/GIP agonist for the treatment of NASH.

Madrigal believes that resmetirom's product profile and expected first-to-market advantage provide meaningful points of differentiation in the NASH competitive landscape.

Commercial Organization

Madrigal has established a commercial leadership team with expertise in launching pharmaceutical products. As of the date of this filing, Madrigal has built out a field sales team and product launch capabilities in anticipation of potential accelerated approval in the U.S. for resmetirom.

Research and Development

Since our inception, we have focused significant resources on our research and development activities. Costs incurred in performing research and development activities include internal costs (including salaries and stock-based compensation); costs for clinical trial consultants, contract research organizations, clinical sites, and other external services; drug manufacturing and supply costs; milestone payments under licensing agreements; other costs of conducting studies including the costs of materials and supplies; the costs associated with seeking regulatory approval; and other costs associated with the Company's preclinical and clinical programs. Please refer to Part II, Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations." of this Annual Report on Form 10-K for a discussion of our research and development expenses incurred during the last three fiscal years.

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, active pharmaceutical ingredients (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 API 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.

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 31, 2023, we own or co-own: seven United States and 44 foreign issued patents; nine United States and 70 foreign pending patent applications; and two international patent applications filed under the Patent Cooperation Treaty. Each of these patents and applications relates to resmetirom, including composition-of-matter, certain polymorph 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 two 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 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 2044, excluding any patent term adjustment that might be available following the grant of the patent. 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.

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.

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 clinical 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;
- preparation and submission to the FDA of an NDA (and the FDA's acceptance for filing of the 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;
- satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCP and the integrity of the clinical data;
- payment of user fees and procurement of FDA approval of the NDA;
- FDA review and approval of the NDA; and
- compliance with any post-approval requirements, including, as applicable, REMS and post-approval studies required by the FDA.

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 initial safety and quality profile 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 suspected adverse reactions, any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol, 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 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:

- *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. In some cases, clinical trials are also monitored by an independent group of qualified experts organized by the trial sponsor. These groups are often referred to as data monitoring committees. This group typically provides recommendations to the trial sponsor for whether or not a trial may move forward at designated check points. These decisions are based on the data monitoring committee's independent review of data from the ongoing trial. 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. In general, sponsors of most interventional clinical trials that are not Phase 1, 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. Sponsors are generally also obligated to disclose the results of these clinical trials after completion. Competitors and others may use this publicly-available information to gain knowledge regarding the design and progress of our development programs.

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 and assuring 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 sponsor under an approved NDA is also subject to annual program user fees. Program fees are assessed for each approved prescription drug product identified in an approved application, with up to five program fees per application. These fees are typically modified annually. 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 the safety or effectiveness of the treatment, prevention or diagnosis of disease may qualify for priority review. Priority review for an NDA for a new molecular entity means the FDA will review the NDA within six months from the date that the NDA is accepted for filing by FDA. 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 21 CFR Part 314, Subpart H accelerated approval pathway if the candidates are intended to treat a serious or life-threatening 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 is thought to predict clinical benefit, such as how a patient feels, functions, or survives, but is not itself a measure of clinical benefit. 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. Approval of a product may be withdrawn if these trials fail to verify clinical benefit or do not demonstrate sufficient clinical benefit to justify the risks associated with the product. 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," the FDA may withdraw approval of the product.

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, the FDA must specify the conditions for any post-approval studies by the date of the accelerated approval and the agency has flexibility in setting forth such conditions, which may include enrollment targets, study protocol and milestones – including the target date of study completion. The 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 additional (i.e., 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 drug and biologic applications and supplements to applications, for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration. Under PREA, such 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 has been assessed to be 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 may send a non-compliance letter to any sponsor that fails to submit the required assessment, maintain a current deferral or 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 or supplement to an approved 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.

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 that meet certain other criteria, 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 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. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. 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 our 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, unless the Competent Authority decides, on justified grounds relating to pharmacovigilance (e.g. exposure of an insufficient number of patients to the medicinal product concerned), to mandate one additional five-year renewal. 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. In April 2023, the European Commission published a proposal to reform the regulatory data protection system in the EU. In the proposal, the 'baseline' of eight years of data exclusivity would be brought back to six years. Additional years of exclusivity can be obtained, but under requirements that are perceived to be more difficult to meet than the current requirements. This proposal is not final yet and it is uncertain if the proposal will be adopted in its current form, and if so, when the revised legislation would enter into force.

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. In 2023, the European Commission published a proposal that intends to reduce the orphan market exclusivity period. However, it is currently uncertain if the proposal will be adopted in its current form and it is uncertain if and when the revised legislation would enter into force.

Coverage and 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 federal and state government authorities, managed care providers, private health insurers and other organizations. Decisions regarding the extent of coverage and amount of reimbursement to be provided are made on a plan-by-plan basis. One third-party payor's decision to cover a product does not ensure that other payors will also provide coverage for the product. 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. 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. A decision by a third-party payor not to cover a product could reduce physician ordering and patient demand for the product.

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. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for a product for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

In addition, sales of our products in other countries are also dependent, in large part, on complex coverage and reimbursement mechanisms and programs in those countries. 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.

U.S. Healthcare Reform

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.

The Inflation Reduction Act of 2022, or IRA, 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.

It is likely that federal and state legislatures and health agencies will continue to focus on additional health care reform measures in the future that will impose additional constraints on prices and reimbursements for our marketed products. 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. There have been several Congressional inquiries and proposed and enacted federal and state legislation and regulatory initiatives designed to, among other things, bring more transparency to product pricing, evaluate the relationship between pricing and manufacturer patient programs, and reform government healthcare program reimbursement methodologies for drug products. Individual states in the U.S. have also increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including by requiring pharmaceutical manufacturers to report to state agencies when they introduce new drugs to market with prices over a certain threshold, or when they increase the price of a drug over a certain threshold. If healthcare policies or reforms intended to curb healthcare costs are adopted, the prices that we charge for any approved product may be limited, our commercial opportunity may be limited and/or our revenues from sales of our product and any future products, if approved, may be negatively impacted.

It is possible that the above-mentioned measures, as currently enacted or may be amended in the future, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, and new payment methodologies and additional downward pressure on coverage and payment and the price that we receive for any approved product. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of additional cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our approved product or products. We cannot be sure whether additional legislative changes will be enacted in the U.S. or outside of the U.S., or whether regulatory changes, guidance or interpretations will be changed, or what the impact of such changes on our product candidates, if any, may be.

Pharmaceutical Price Reporting

A number of government pricing programs create certain price reporting obligations. Under the Medicaid Drug Rebate program, a participating manufacturer is required to pay a rebate to each state Medicaid program for its covered outpatient drugs that are dispensed to Medicaid beneficiaries and paid for by the state Medicaid program as a condition of having federal funds being made available for drugs under Medicaid and Medicare Part B. Those rebates are based on pricing data reported by the manufacturer on a monthly and quarterly basis to CMS. These data include the average manufacturer price and, in the case of innovator products, the best price for each drug, which, in general, represents the lowest price available from the manufacturer to any wholesaler, retailer, provider, health maintenance organization, nonprofit entity, or governmental entity in the U.S. in any pricing structure, calculated to include all sales and associated rebates, discounts, and other price concessions.

The ACA (addressed further above in the section on "-- U.S. Healthcare Reform") made significant changes to the Medicaid Drug Rebate Program, and CMS issued a final regulation to implement the changes to the Medicaid Drug Rebate Program under the ACA. CMS also issued a final regulation that modified prior Medicaid Drug Rebate Program regulations to permit reporting multiple best price figures with regard to value based purchasing arrangements; and provide definitions for "line extension," "new formulation," and related terms, with the practical effect of expanding the scope of drugs considered to be line extensions that are subject to an alternative rebate formula.

Federal law requires that a manufacturer also participate in the 340B Drug Pricing program in order for federal funds to be available for the manufacturer's drugs under Medicaid and Medicare Part B. The 340B program requires participating manufacturers to agree to charge no more than the 340B "ceiling price" for the manufacturer's covered outpatient drugs to a specified "covered entities," including community health centers and other entities that receive certain federal grants, as well as hospitals that serve a disproportionate share of low-income patients. The 340B ceiling price is calculated using a statutory formula, which is based on the average manufacturer price and rebate amount for the covered outpatient drug as calculated under the Medicaid Drug Rebate Program.

Further, the IRA establishes a Medicare Part D inflation rebate schemes (the first rebate period is in fourth quarter 2022 through third quarter 2023) and a drug price negotiation program, with the first negotiated prices to take effect in 2026. It also makes several changes to the Medicare Part D benefit, including the creation of a new manufacturer discount program in place of the current coverage gap discount program (beginning in 2025).

Finally, 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 participate in the VA Federal Supply Schedule ("FSS") pricing program, established under Section 603 of the Veterans Health Care Act of 1992. Under this program, the manufacturer is obligated to make its covered drugs available for procurement on an 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. The FCP is derived from a calculated price point called the "non-federal average manufacturer price" ("Non FAMP"), which the manufacturer calculates and reports to the VA on a quarterly and annual basis. Pursuant to applicable law, knowing provision of false information in connection with a Non FAMP filing can subject a manufacturer to significant penalties for each item of false information. The FSS contract also contains extensive disclosure and certification requirements. 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. The rebates are calculated as the difference between the annual Non FAMP and FCP for the calendar year that the product was dispensed.

Human Capital

As of February 22, 2024, we had 376 full-time employees, including 99 engaged in research, development, and regulatory activities, and 277 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 2024 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, 2023, we had an accumulated deficit of approximately $1,336.3 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, 2023, we had cash, cash equivalents and marketable securities of approximately $634.1 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. 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 for potential use in non-alcoholic steatohepatitis, or NASH. Successful 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 and commercial development of resmetirom. The future success of resmetirom is subject to a number of risks, including the following:

- a delay, or inability to reach agreement with the FDA, concerning approval of resmetirom;
- regulators, IRBs or ethics committees may not authorize us or our investigators to continue to conduct ongoing trials or complete a clinical trial;
- we may not be able to demonstrate or obtain adequate evidence from clinical trials of efficacy and safety for resmetirom;
- we do not know the degree to which resmetirom will be accepted as a therapy by physicians, patients and payors, even if approved;
- commercial execution risks;
- 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 clinical development;
- we cannot be certain if we will be able to gain full approval of our product candidate following any Subpart H approval based on surrogate endpoints; and
- even if we obtain Subpart H approval of resmetirom based on a surrogate endpoint, we are required to conduct complete the 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 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 completion of clinical trials may also ultimately lead to the adverse regulatory action. Further, the FDA, EMA or other regulatory authorities may disagree with our clinical trial design for ingoing trials 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. Any delays in our clinical development programs may harm our business, financial condition and results of operations significantly.

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. If we are unable to obtain regulatory approval for, or, if approved, successfully commercialize resmetirom, we may not be able to generate sufficient revenue to continue our business.

If approved, we will be highly dependent on the commercial success of resmetirom. We may not be able to meet expectations with respect to sales of our products if approved by the FDA, or attain profitability and positive cash-flow from operations.

We have received breakthrough therapy designation and priority review from the FDA for resmetirom for the treatment of patients with NASH with liver fibrosis, and FDA has assigned a Prescription Drug User Fee Act date for resmetirom of March 14, 2024, the target date by which the FDA intends to complete its review and take action on the NDA. If resmetirom receives FDA approval, the success of our business will depend on the commercial success of resmetirom.

Successful commercialization of resmetirom, if approved, is subject to many risks. We have never, as an organization, launched or commercialized any other product, and there is no guarantee that we will be able to successfully commercialize resmetirom if approved. There are numerous examples of failures to meet high expectations of market potential, including by pharmaceutical companies with more experience and resources than us. We expect that future commercial success of resmetirom for the treatment of patients with NASH will depend on many factors, including the following:

- the efficacy, cost, approved use, and side-effect profile of resmetirom relative to competitive treatment regimens, if approved, for the treatment of NASH;
- if approved for NASH, resmetirom may compete with the off-label use of currently marketed products and other therapies in development that may in the future obtain approval for NASH;
- the effectiveness of our commercial strategy for the marketing of resmetirom, including our pricing strategy and the effectiveness of our efforts to obtain adequate third-party reimbursements;
- developing, maintaining and successfully monitoring commercial manufacturing arrangements for resmetirom with third-party manufacturers to ensure they meet our standards and those of regulatory authorities, including the FDA, which extensively regulate and monitor pharmaceutical manufacturing facilities;
- our ability to negotiate and enter into any additional commercial, supply and distribution contracts to support commercialization efforts, and to hire and manage additional qualified personnel;
- our ability to meet the demand for commercial supplies of resmetirom at acceptable costs;
- the acceptance of resmetirom by physicians, patients and third-party payors;

- our ability to remain compliant with laws and regulations that apply to us and our commercial activities;
- the actual market-size, ability to identify targeted patients and the demographics of patients eligible for resmetirom, which may be different than what we currently expect;
- the occurrence of any side effects, adverse reactions or misuse, or any unfavorable publicity in these areas;
- our ability to obtain, maintain or enforce our patents and other intellectual property rights; and
- the effect of recent or potential health care legislation in the United States.

While we believe that resmetirom for the treatment of NASH, if approved, should have a commercially competitive profile, we cannot accurately predict the amount of time needed to attain a commercially successful profile or the amount of revenue that would be generated from the sale of resmetirom. If we do not effectively commercialize resmetirom, we will not be able to execute our business plan and may not be able to achieve profitability. If our revenues, market share and/or other indicators of market acceptance of resmetirom do not meet the expectations of investors or public market analysts, the market price of our common stock would likely decline.

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. 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 for our MAESTRO-NASH Outcomes trial is not complete as of December 31, 2023 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.

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.

Breakthrough therapy or priority review by the FDA for any product candidate may not lead to faster development, regulatory review or approval processes, and it does not increase the likelihood that our product candidates will receive marketing approval.

We have received breakthrough therapy designation and priority review from the FDA for resmetirom for the treatment of patients with NASH with liver fibrosis, and we may seek breakthrough therapy designation or priority review for future product candidates if supported by the results of clinical trials. A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Priority review is intended to speed the FDA marketing application review timeframe for drugs that treat a serious condition and, if approved, would provide a significant improvement in safety or effectiveness.

For drugs and biologics that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development. Sponsors of drugs that are breakthrough therapies may also be able to submit marketing applications on a rolling basis, meaning that the FDA may review portions of a marketing application before the sponsor submits the complete application to the FDA, if the sponsor pays the user fee upon submission of the first portion of the marketing application. For applications that receive priority review, the FDA's marketing application review goal is shortened to six months, as opposed to ten months under standard review.

Designation as a breakthrough therapy or priority review product is within the discretion of the regulatory agency. Accordingly, even if we believe one of our future product candidates meets the criteria for designation as a breakthrough therapy or priority review product, the agency may disagree and instead determine not to make such designation. In any event, the receipt of such a designation for a product candidate may not result in a faster development process, review or approval compared to drugs considered for approval under conventional regulatory procedures and does not assure ultimate marketing approval by the agency. In addition, regarding breakthrough therapies, the FDA may later decide that the products no longer meet the conditions for qualification as a breakthrough therapy or, for priority review products, decide that the period for FDA review or approval will not be shortened.

Even if resmetirom or any product candidate receives accelerated approval from the FDA, they face future post-approval development and regulatory requirements, which present additional challenges for us to successfully navigate.

We are currently pursuing accelerated approval of our lead product candidate, resmetirom. Under the accelerated approval pathway, continued approval may be contingent upon verification of a clinical benefit in confirmatory trials. These post-approval requirements and commitments may not be feasible and/or could impose significant burdens and costs on us; could negatively impact our development, manufacturing and supply of our products; and could negatively impact our financial results. Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval. Failure to meet post-approval commitments and requirements, including completion of enrollment of—and in particular, any failure to obtain positive data from—any confirmatory studies required by the FDA, could result in negative regulatory action from the FDA and/or withdrawal of such accelerated approval. The recently enacted FDORA has expanded FDA's expedited withdrawal procedures for drugs approved through the accelerated approval pathway if a sponsor fails to conduct any required post-approval study with due diligence.

Unless otherwise informed by the FDA, an applicant must submit to the FDA for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the FDA, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement. If we or the manufacturing facilities for our products fail to comply with applicable regulatory requirements, the FDA may, among other actions: issue warning letters or untitled letters; seek an injunction or impose civil or criminal penalties or monetary fines; suspend or withdraw or alter the conditions of our marketing approval; suspend any ongoing clinical trials;

refuse to approve pending applications or supplements to applications submitted by us; suspend or impose restrictions on operations, including costly new manufacturing requirements; and seize or detain products, refuse to permit the import or export of products or require us to initiate a product recall.

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.

Resmetirom has only been studied in a limited number of patients. Following commercial launch, if approved, resmetirom will be available to a much larger number of patients, and we do not know whether the results of resmetirom's use in such larger number of patients will be consistent with the results from our clinical studies.

Resmetirom has been administered only to a relatively limited number of patients in clinical studies. While the FDA may grant accelerated approval of resmetirom based on the data included in the NDA, we do not know whether future results, when a large number of patients are exposed to resmetirom including results related to safety and efficacy, will be consistent with the results from earlier clinical studies of resmetirom that served as the basis for the approval of resmetirom. New data relating to resmetirom, including from adverse event reports, our post-marketing commitments in the United States, and from other ongoing clinical studies, may result in changes to the product label and may adversely affect sales, or result in withdrawal of resmetirom from the market. The FDA and regulatory authorities in other jurisdictions may also consider the new data in reviewing resmetirom's marketing applications for additional indications and/or in other

jurisdictions, or impose post-approval requirements. If any of these actions were to occur, it could result in significant expense and delay or limit our ability to generate sales revenues.

If payers excessively restrict our future products or 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, our ability to generate revenues will be impacted.

Even if any of our product candidates obtain regulatory approval, they may not gain extensive 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 fully 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 or a patient though prescribed our product may not receive it 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;
- restrictions in the label of the drug;
- other potential advantages of alternative treatment methods;
- unanticipated post-marketing events;
- ineffective marketing and distribution support of its products;
- inability of third-party patient services to achieve patient access to therapy; and
- inability of specialty pharmacies to communicate effectively with patients, coordinate shipments and effect adherence to therapy.

If any of our product candidates are approved, but fail to achieve full 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, including successfully optimizing manufacturing for our product/product candidate in sufficient quality and quantity or within targeted timelines.

As we have been advancing resmetirom through clinical trials, we have been expanding our development, regulatory, manufacturing, and marketing and sales capabilities and commitments 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, and marketing personnel, effectively manage our participation in ongoing clinical trials 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 (such as ex-US arrangements or arrangements described in the succeeding section) 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.

If we are unable to successfully further develop and maintain internal commercialization capabilities, future sales of our products, if approved, may be negatively impacted.

In anticipation of potential regulatory approval of resmetirom, we have been hiring and training a commercial team and developing the organizational infrastructure we believe we need to support the commercial success of resmetirom. Factors that may inhibit our efforts to maintain and further develop commercial capabilities include:

- an inability to retain an adequate number of effective commercial personnel;
- an inability to adequately train commercial personnel, who may have limited experience with our company or our products, to deliver a consistent message regarding our products and be effective in educating physicians on how to prescribe our products;
- an inability to equip commercial field personnel with compliant and effective materials, including marketing literature to help them educate physicians and our healthcare providers regarding our products and their proper administration and educate payors on the safety, efficacy and effectiveness profile of our products to support favorable coverage decisions; and
- unforeseen costs and expenses associated with maintaining and further developing an independent commercial organization.

If we are not successful in maintaining an effective commercial infrastructure, we will encounter difficulty in achieving, maintaining or increasing projected sales of resmetirom once approved, which would adversely affect our business and financial position.

In addition, we may in the future 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.

The insurance coverage and reimbursement status of newly-approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for new or current products could limit our ability to market those products and decrease our ability to generate revenue.

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.

The future pricing, coverage and reimbursement of our product candidates must be adequate to support our commercial infrastructure. Our future per-patient prices must be sufficient to recover our development and manufacturing costs and potentially achieve profitability. However, sales of any pharmaceutical product depend, in part, on the extent to which such product will be covered by third-party payors, such as federal, state, and foreign government healthcare programs, commercial insurance and managed healthcare organizations, and the level of reimbursement for such product by third-party payors. Significant uncertainty exists as to the coverage and reimbursement status of any newly approved product. Decisions regarding the extent of coverage and amount of reimbursement to be provided are made on a plan-by-plan basis. One third-party payor's decision to cover a product does not ensure that other payors will also provide coverage for the product. As a result, we do not have assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance or in the future.

In addition, third-party payors have increasingly reduced reimbursements for pharmaceutical products. The U.S. government and state legislatures have continued implementing cost-containment programs, including price controls, restrictions on coverage and reimbursement, and requirements for substitution of generic products. Third-party payors are increasingly challenging the prices charged, examining the medical necessity, and reviewing the cost effectiveness of pharmaceutical products, in addition to questioning their safety and efficacy. Increasingly, third-party payors are requiring

that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. Further, such payors are increasingly challenging the price, examining the medical necessity and reviewing the cost effectiveness of medical product candidates. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit or delay sales of any of our future products. A decision by a third-party payor not to cover a product could reduce physician ordering and patient demand for any of our future products.

In international markets, reimbursement and healthcare payment are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost-containment initiatives in the European Union, Canada and other countries will put pressure on the pricing and usage of our product candidates. In many countries, the prices of medicinal products are subject to varying price control mechanisms as part of national health systems. In general, the prices of therapeutics or medicinal products under such systems are substantially lower than in the U.S. For example, the European Union provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. Furthermore, there is no assurance that a product will be considered medically reasonable and necessary for a specific indication, will be considered cost-effective by third-party payors, that an adequate level of reimbursement will be established even if coverage is available, or that the third-party payors' reimbursement policies will not adversely affect the ability of manufacturers to sell products profitably. Accordingly, in markets outside the U.S., the reimbursement for our products may be reduced compared with the U.S. and may be insufficient to generate commercially reasonable revenue and profits.

The pricing of pharmaceutical products has come under increasing scrutiny as part of a global trend toward healthcare cost containment. Resulting changes in healthcare law and policy, including recently enacted changes to Medicare, may impact our business in ways that we cannot currently predict, which could have a material adverse effect on our business and financial condition.

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.

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 Patient Protection and Affordable Care Act, as amended, (the ACA) aims 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.

In addition to the ACA, U.S. governments continue to seek to adopt healthcare policies and reforms intended to curb healthcare costs, such as federal or state controls on payment for drugs (including under Medicare, Medicaid, and commercial health plans). The Inflation Reduction Act of 2022, or IRA, 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.

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. Additionally, there have been several Congressional inquiries and proposed and enacted federal and state legislation and regulatory initiatives designed to, among other things, bring more transparency to product pricing, evaluate the relationship between pricing and manufacturer patient programs, and reform government healthcare program reimbursement methodologies for drug products. Individual states in the U.S. have also increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including by requiring pharmaceutical manufacturers to report to state agencies when they introduce new drugs to market with prices over a certain threshold, or when they increase the price of a drug over a certain threshold. If healthcare policies or reforms intended to curb healthcare costs are adopted, the prices that we charge for any approved products may be limited, our commercial opportunity may be limited and/or our revenues from sales of our product and any future products, if approved, may be negatively impacted.

It is possible that the above-mentioned measures, as currently enacted or may be amended in the future, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, and new payment methodologies and additional downward pressure on coverage and payment and the price that we receive for any approved product. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of additional cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our products. We cannot be sure whether additional legislative changes will be enacted in the U.S. or outside of the U.S., or whether regulatory changes, guidance or interpretations will be changed, or what the impact of such changes on our product candidates, if any, may be.

If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate program or other governmental pricing programs after we begin participating in these programs, we could be subject to additional rebate requirements, penalties, or other sanctions, which could have a material adverse effect on our business, financial condition, results of operations, and growth prospects.

Under the Medicaid Drug Rebate program, a participating manufacturer is required to pay a rebate to each state Medicaid program for its covered outpatient drugs that are dispensed to Medicaid beneficiaries and paid for by the state Medicaid program as a condition of having federal funds being made available for drugs under Medicaid and Medicare Part B. Those rebates are based on pricing data reported by the manufacturer on a monthly and quarterly basis to CMS. These data include the average manufacturer price and, in the case of innovator products, the best price for each drug, which, in general, represents the lowest price available from the manufacturer to any wholesaler, retailer, provider, health maintenance organization, nonprofit entity, or governmental entity in the U.S. in any pricing structure, calculated to include all sales and associated rebates, discounts, and other price concessions. If we fail to pay the required rebate amount or report pricing data on a timely basis, we may be subject to civil monetary penalties and/or termination from the Medicaid Drug Rebate program. Additionally, civil monetary penalties can be applied if we are found to have knowingly submitted any false price or product information to the government, if we fail to submit the required price data on a timely basis, or if we misclassify or misreport product information. CMS could also decide to terminate our Medicaid drug rebate agreement, in which case federal payments may not be available under Medicaid or Medicare Part B for our covered outpatient drugs.

The ACA (addressed further above in the section on "-- U.S. Healthcare Reform") made significant changes to the Medicaid Drug Rebate Program, and CMS issued a final regulation to implement the changes to the Medicaid Drug Rebate Program under the ACA. CMS also issued a final regulation that modified prior Medicaid Drug Rebate Program regulations to permit reporting multiple best price figures with regard to value based purchasing arrangements; and provide definitions for "line extension," "new formulation," and related terms, with the practical effect of expanding the scope of drugs considered to be line extensions that are subject to an alternative rebate formula. Our failure to comply with these price reporting and rebate payment options, as well as pharmaceutical benefit manager "accumulator" programs, could negatively impact our financial results.

Federal law requires that a manufacturer also participate in the 340B Drug Pricing program in order for federal funds to be available for the manufacturer's drugs under Medicaid and Medicare Part B. The 340B program requires participating manufacturers to agree to charge no more than the 340B "ceiling price" for the manufacturer's covered outpatient drugs to a specified "covered entities," including community health centers and other entities that receive certain federal grants, as well as hospitals that serve a disproportionate share of low-income patients. The 340B ceiling price is calculated using a

statutory formula, which is based on the average manufacturer price and rebate amount for the covered outpatient drug as calculated under the Medicaid Drug Rebate Program. If we are found to have knowingly and intentionally charged 340B covered entities more than the statutorily mandated ceiling price, we could be subject to significant civil monetary penalties and/or such failure also could be grounds for HRSA to terminate our agreement to participate in the 340B program, in which case our covered outpatient drugs would no longer be eligible for federal payment under the Medicaid or Medicare Part B program.

Further, the IRA established a Medicare Part D inflation rebate scheme and a drug price negotiation program, with the first negotiated prices to take effect in 2026. It also makes several changes to the Medicare Part D benefit, including the creation of a new manufacturer discount program in place of the current coverage gap discount program (beginning in 2025). Manufacturers may be subject to civil monetary penalties for certain violations of the negotiation and inflation rebate provisions and an excise tax during a noncompliance period under the negotiation program. Drug manufacturers may also be subject to civil monetary penalties with respect to their compliance with the new Part D manufacturer drug discount program.

Pricing and rebate calculations are complex, vary across products and programs, and are often subject to interpretation by the manufacturer, governmental agencies, and courts. A manufacturer that becomes aware that its Medicaid reporting for a prior quarter was incorrect, or has changed as a result of recalculation of the pricing data, is obligated to resubmit corrected data up to three years after those data originally were due. Restatements and recalculations increase the costs for complying with the laws and policies governing the Medicaid Drug Rebate program and could result in an overage or underage in our rebate liability for past quarters. They also may affect the 340B ceiling price and therefore liability under the 340B program.

Finally, 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 participate in the VA Federal Supply Schedule ("FSS") pricing program, established under Section 603 of the Veterans Health Care Act of 1992. Under this program, the manufacturer is obligated to make its covered drugs available for procurement on an 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. The FCP is derived from a calculated price point called the "non-federal average manufacturer price" ("Non FAMP"), which the manufacturer calculates and reports to the VA on a quarterly and annual basis. Pursuant to applicable law, knowing provision of false information in connection with a Non FAMP filing can subject a manufacturer to significant penalties for each item of false information. The FSS contract also contains extensive disclosure and certification requirements. If we overcharge the government in connection with the FSS contract or Tricare Retail Pharmacy Rebate Program, whether due to a misstated FCP or otherwise, we will be required to refund the difference to the government. Failure to make necessary disclosures and/or to identify contract overcharges can result in allegations against us under the False Claims Act and other laws and regulations. Unexpected refunds to the government, and any response to government investigation or enforcement action, would be expensive and time-consuming, and could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

Under Section 703 of the National Defense Authorization Act, a 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. The rebates are calculated as the difference between the annual Non FAMP and FCP for the calendar year that the product was dispensed. A manufacturer that overcharges the government in connection with the FSS contract or Tricare Retail Pharmacy Rebate Program, whether due to a misstated FCP or otherwise, is required to refund the difference to the government. Failure to make necessary disclosures and/or to identify contract overcharges can result in allegations against us under the False Claims Act and other laws and regulations.

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. 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 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 senior management personnel, it could have a material adverse effect on our business and stock price.

We are highly dependent on principal members of our senior management team, including our President and Chief Executive Officer, Bill Sibold, 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 senior member of our management team or scientific staff, including Mr. Sibold or Dr. Taub, could have a material adverse effect on our business and stock price. 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.

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.

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; inaccurately 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.

A failure of our information technology infrastructure and cybersecurity threats may adversely affect our business and operations.

Our information technology infrastructure is subject to threats from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. In addition, the information technology systems of our current or future third-party collaborators, service providers, contractors and consultants are subject to similar threats, and we depend in part on third-party security measures over which we do not have full control to protect against data security incidents. 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 potentially extracting sensitive information, such as trade secrets or other intellectual property, such attacks could include the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering and other means, including ransom demands, to affect service reliability and/or threaten the confidentiality, integrity and availability of information. Such an event could result in a material disruption of our operations or development programs and/or produce significant reputational, financial, legal, regulatory, business or operational harm. For example, any loss of clinical trial data 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. We have been subject to a cybersecurity attack in the past. Although we have taken steps to enhance our cybersecurity protections and minimize the impact of any future event, we cannot provide any assurances that future cyber events will not occur, that these security safeguards will be successful, and that future cyber events, to the extent they occur, will not impact our operations or have any material adverse impact on our business. As a result, we may not in the future successfully prevent service interruptions, exfiltrations or data security incidents that could materially adversely affect our business. In addition, insurance may not cover or be sufficient in type or amount to cover us against claims related cyber incidents.

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, litigation, regulatory enforcement actions, fines, sanctions or other penalties, injunctive relief requiring costly compliance measures, required notification and credit monitoring, public statements against us, third parties to lose trust in us, or 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 cybersecurity attacks can be difficult to detect, and any delay in identifying them may lead to increased harm.

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 implementing regulations continue 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 have enacted similar laws that impose 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, Indiana, Iowa, Tennessee, Washington, and 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 including as implemented in the UK (collectively, "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, places certain obligations on the processing of such personal data including ensuring the lawfulness of processing personal data, 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 where applicable, 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 European 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 between companies certified under the new framework.

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 the future. We expect our overall spending levels to increase. The amount and timing of any expenditure needed to fund our development and commercialization programs will depend on numerous factors, including:

- the type, number, scope, progress, expansion costs, results of and timing of our ongoing and future clinical trials and projected product label or the need for additional clinical trials ;
- the costs of obtaining, maintaining and enforcing our patents and other intellectual property rights;
- the timing of obtaining regulatory approval for resmetirom for NASH and any potential future product candidates;
- the costs and timing of obtaining or maintaining manufacturing for resmetirom for NASH, including commercial manufacturing if such product candidate is approved;
- the costs and timing of establishing and initiating sales, marketing and reimbursement capabilities and enhanced internal controls over financial and compliance reporting requirements;
- 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. 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 prior to the filing of this Form 10-K, and we cannot estimate the amounts of any revenue from any product sales, if approved, in the 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, our business may be materially and adversely affected. 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 Capital, Inc. ("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 $58.39 to $312.00 per share during the period from December 1, 2022 to January 31, 2024. 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 beneficially 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 beneficially own approximately 24.24% of our outstanding common stock as of December 31, 2023 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.

Funds affiliated with Baker Bros. Advisors LP hold a significant portion of our total outstanding shares of common stock (including shares of our common stock issuable upon conversion of shares of our Series A Convertible Preferred Stock and Series B Convertible Preferred Stock and pre-funded warrants), and any sale of such shares into the market,

or perception that sales could occur, in the future could cause the market price of our common stock to drop significantly.

Based on a Schedule 13D/A filed with the SEC on November 17, 2023, 667, L.P. and Baker Brothers Life Sciences, L.P., funds affiliated with Baker Bros. Advisors LP ("Baker Bros."), reported an ownership interest in (i) Madrigal common stock and (ii) other Madrigal securities with limitations on conversion or exercise to common stock. If such limitations did not exist, Baker Bros. would be deemed to beneficially own 5,851,323 shares of our common stock (which includes 1,969,797 shares of common stock issuable upon the conversion of our Series A Convertible Preferred Stock and 400,000 shares of common stock issuable upon the conversion of our Series B Convertible 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, which may be increased or decreased up to 19.99% at the holder's election on 61 days' notice and certain limitations (the "Beneficial Ownership Limitation"). The 5,851,323 total share number above includes 1,648,098 pre-funded warrants and without such limitations on conversion or exercise would represent approximately 24.49% of our total outstanding shares of common stock as of December 31, 2023 on a fully as-converted and as-exercised to common stock basis. The pre-funded warrants are only exercisable to the extent that after giving effect to such exercise the holders thereof, together with their affiliates and any members of a Section 13(d) group with such holders, would beneficially own, for purposes of Rule 13d-3 under the Exchange Act, no more than 9.99% of the outstanding shares of Common Stock (the "Maximum Percentage"). By written notice to us, holders of the pre-funded warrants may from time to time increase or decrease the Maximum Percentage to any other percentage not in excess of 19.99%. Sales of a substantial number of shares of our common stock in the public market by Baker Bros., or the perception that these sales might occur, could depress the market price of our common stock and could impair our ability to raise capital through the sale of additional equity securities. We are unable to predict the effect that sales by Baker Bros., or any perception that sales may occur, may have on the prevailing market price of our common stock.

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, 2023, there were a number of investors or investor groups that held a significant beneficial ownership interest in our common stock. Drs. Paul Friedman and Becky Taub (the "Friedman/Taub Holdings"), a director and President of R&D and Chief Medical Officer, respectively collectively beneficially own 2,212,070 shares (or 10.62%) of our common stock. Based on a Schedule 13D/A filed with the SEC on November 17, 2023, funds affiliated with Baker Bros. Advisors LP beneficially owned (for SEC reporting purposes) 9.99% of our common stock and maintained an ownership interest in up to 5,851,323 shares of our common stock subject to exercise or conversion limits such as the Beneficial Ownership Limitation and Maximum Percentage (the "Baker Bros. Holdings"), as described in the preceding paragraph. Based on a Schedule 13G/A filed with the SEC on February 14, 2024, funds affiliated with Avoro Capital Advisors LLC (the "Avoro Holdings") reported beneficial ownership of 2,288,888 shares of our Common Stock, including pre-funded warrants to purchase 400,000 shares of Common Stock that are subject to the Maximum Percentage. In addition, as of December 31, 2023, there are: 2,881,896 shares of our common stock issuable upon the exercise of outstanding stock options or the vesting of restricted stock units and performance stock units under our 2015 Stock Plan, as amended and 2023 Inducement Plan; pre-funded warrants to purchase shares of Common Stock pursuant to outstanding pre-funded warrants as described above; and 19,454 shares of our common stock issuable upon the exercise of outstanding vested warrants held by our creditors consisting of Hercules and affiliates. In addition, there are other institutional investors (including funds affiliated with Janus Henderson Group plc, which reported beneficial ownership of 2,902,050 shares of our common stock, or 14.7%, in a Schedule 13G/A filed with the SEC on February 13, 2024) who from time to time file Schedule 13Gs (or amendments thereto) or Form 13Fs reflecting substantial beneficial ownership of outstanding common stock.

Sales of a substantial number of shares of our common stock by one or more of the investors or groups listed above or other equity-related securities in the public markets, could depress the market price of our common stock and impair our ability to raise capital. 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 1C. Cybersecurity

We are increasingly dependent on sophisticated software applications and computing infrastructure to conduct key operations. We depend on both our own systems, networks, and technology as well as the systems, networks and technology of our contractors, consultants, vendors and other business partners.

Cybersecurity Program

Given the importance of cybersecurity to our business, we maintain a cybersecurity program to support both the effectiveness of our systems and our preparedness for information security risks. This program includes a number of administrative, physical, and technical safeguards. We have conducted and plan to conduct evaluations of our cybersecurity program through periodic internal and external audits, penetration tests, and incident response simulations. We also require cybersecurity trainings when onboarding new employees and contractors/other workforce members, as well as annual cybersecurity awareness training for our employees and contractors/other workforce members. Our program is based on industry frameworks, including the National Institute of Standards and Technology (NIST) Cybersecurity Framework (CSF) to strengthen our program effectiveness and reduce cybersecurity risks.

We use a risk-based approach with respect to our use and oversight of third-party service providers, tailoring processes according to the nature and sensitivity of the data accessed, processed, or stored by such third-party service provider and performing additional risk screenings and procedures, as appropriate. We use a number of means to assess cyber risks related to our third-party service providers, including vendor questionnaires/conducting due diligence in connection with onboarding new vendors and ongoing reviews / due diligence with key third-party vendors. We also seek to collect and assess cybersecurity audit reports and other supporting documentation when available and include appropriate security terms in our contracts where applicable as part of our oversight of third party providers.

Process for Assessing, Identifying and Managing Material Risks from Cybersecurity Threats

In the event of a cybersecurity incident, we maintain a regularly tested incident response program. Pursuant to the program and its escalation protocols, designated personnel are responsible for assessing the severity of an incident and associated threat, containing the threat, remediating the threat, including recovery of data and access to systems, analyzing any reporting obligations associated with the incident, and performing post-incident analysis .

We have relationships with a number of third-party service providers to assist with cybersecurity containment and remediation efforts.

Governance

Management Oversight

The controls and processes employed to assess, identify and manage material risks from cybersecurity threats are implemented and overseen by our Chief Information Officer (“CIO”). Our CIO has more than 25 years of digital experience in the biopharmaceutical industry and was previously Senior Vice President Digital at Moderna, Inc., where he was responsible for technology leadership and digital transformation across core operations. Our CIO is responsible for the day-to-day management of the cybersecurity program, including the prevention, detection, investigation, response to, and recovery from cybersecurity threats and incidents, and are regularly engaged to help ensure the cybersecurity program functions effectively in the face of evolving cybersecurity threats. Our CIO provides regular briefings for our senior management team on cybersecurity matters, including threats, events, and program enhancements.

Board Oversight

While the Board of Directors has overall responsibility for risk oversight, our Audit Committee oversees cybersecurity risk matters. The Audit Committee is responsible for reviewing, discussing with management, and overseeing the Company's data privacy, information technology and security and cybersecurity risk exposures, including: (i) the potential impact of those exposures on the Company's business, financial results, operations and reputation; (ii) the programs and steps implemented by management to monitor and mitigate any exposures; (iii) the Company's information governance and cybersecurity policies and programs; and (iv) major legislative and regulatory developments that could materially impact the Company's data privacy and cybersecurity risk exposure. On a quarterly basis, our General Counsel, Chief Financial Officer ("CFO") and CIO have been and are responsible to report to the Audit Committee on information technology and cybersecurity matters, including key risks, a detailed threat assessment relating to information technology risks, as applicable, the potential impact of those exposures on the Company's business, financial results, operations and reputation, the programs and steps implemented by management to monitor and mitigate exposures, and significant legal developments that could materially impact the Company's cybersecurity risk exposure.

Cybersecurity Risks

Our cybersecurity risk management processes are integrated into our overall Enterprise Risk Management ("ERM") process. As part of our ERM process, department leaders identify, assess and evaluate risks impacting our operations across the Company, including those risks related to cybersecurity. While we believe we maintain an effective cybersecurity program, the techniques used to infiltrate information technology systems continue to evolve. Accordingly, we may not be able to timely detect threats or anticipate and implement adequate security measures. For additional information, see "Item 1A—Risk Factors; A failure of our information technology infrastructure and cybersecurity threats may adversely affect our business and operations."

We also maintain cybersecurity insurance providing coverage for certain costs related to cybersecurity-related incidents that impact our own systems, networks, and technology.

Since January 1, 2021 (the first date covered by the financial statements presented in this Form 10-K), we have not experienced any material cybersecurity incident.

Item 2. Properties

As of December 31, 2023, 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, 2026. 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.

Holders

As of December 31, 2023, there were approximately 28 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 and three holders of our pre-funded warrants.

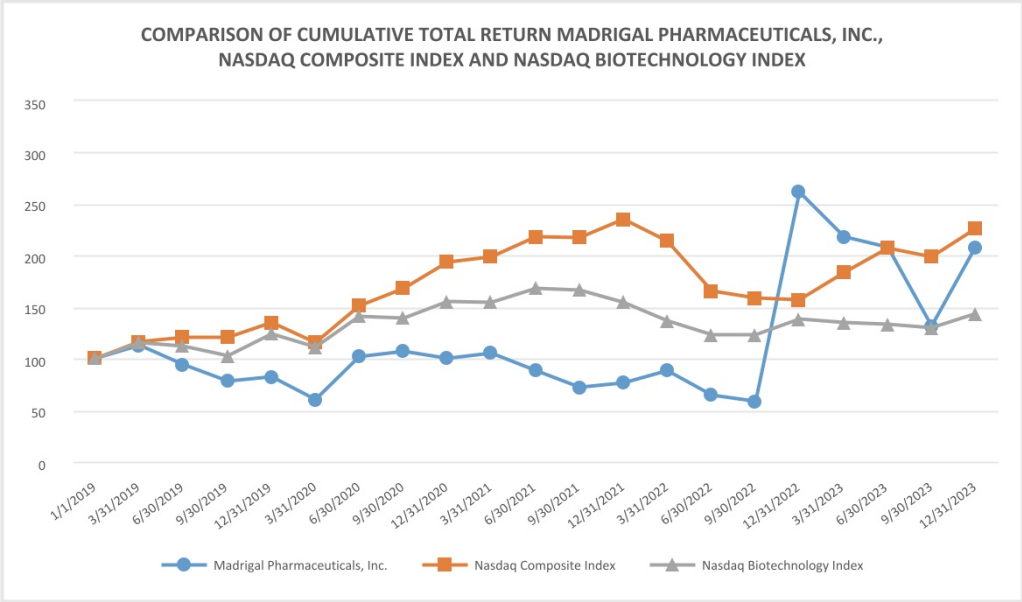
Dividends

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, 2019 and December 31, 2023, 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, 2019 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.

About Madrigal Pharmaceuticals, Inc.

We are a clinical-stage biopharmaceutical company pursuing novel therapeutics for nonalcoholic steatohepatitis, or NASH, a liver disease with high unmet medical need. Our lead candidate, resmetirom, is a once-daily, oral, liver-directed thyroid hormone receptor-ß (THR-ß), agonist designed to target key underlying causes of NASH.

NASH Disease State Overview. NASH is a more advanced form of nonalcoholic fatty liver disease (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. NASH is the leading cause of liver transplants in the U.S. for women, and is expected to soon be the leading cause of liver transplants overall. Additionally, patients with NASH, especially those with more advanced metabolic risk factors (hypertension, concomitant type 2 diabetes), are at increased risk for adverse cardiovascular events and increased morbidity and mortality. Once patients progress to NASH with significant fibrosis (consistent with fibrosis stages 2 and 3), the risk of adverse liver outcomes increases substantially.

NASH is also known as metabolic dysfunction-associated steatohepatitis ("MASH") following a change in disease nomenclature introduced by hepatology medical societies in 2023.

Our Patient Focus. Madrigal estimates that approximately 1.5 million patients have been diagnosed with NASH in the U.S., of which approximately 525,000 have NASH with significant fibrosis. Madrigal estimates that approximately 315,000 diagnosed patients with NASH with significant fibrosis are under the care of the liver specialist physicians Madrigal will be targeting during the planned launch of resmetirom following approval.

Our Clinical Development Program. Madrigal is currently conducting multiple Phase 3 clinical trials to evaluate the safety and efficacy of resmetirom for the treatment of NASH, including the pivotal MAESTRO-NASH biopsy study in patients with significant fibrosis, the MAESTRO-NASH Outcomes study in patients with NASH with compensated cirrhosis and the MAESTRO-NAFLD-1 safety study. Positive results from the pivotal MAESTRO-NASH biopsy study were published in the *New England Journal of Medicine* in February 2024.

Data from the 52-week first 1,000 patient portion of MAESTRO-NASH, together with data from MAESTRO-NAFLD-1, the open-label extension of the MAESTRO-NAFLD-1 study, Phase 2 and Phase 1 data, including safety parameters, formed the basis for Madrigal's subpart H submission to the FDA for accelerated approval of resmetirom for treatment of NASH with liver fibrosis.

Key Developments

In February 2024, primary results from the MAESTRO-NASH study were published in the *New England Journal of Medicine.*

In September 2023, Madrigal announced we had commenced a public underwritten offering of common stock and pre-funded warrants to purchase common stock (the "Offering"). The Offering closed in October 2023. We received gross proceeds totaling $500.0 million. Our net proceeds were $472.0 million, after deducting fees and commissions. We intend to use the net proceeds from the Offering for our clinical and commercial activities in preparation for a potential launch of resmetirom in the U.S. and for general corporate purposes, including, without limitation, research and development expenditures, clinical trial expenditures, manufacture and supply of drug substance and drug products, potential acquisitions or licensing of new technologies, capital expenditures and working capital.

Also in September 2023, Madrigal announced our Board of Directors (the "Board") appointed Bill Sibold as the President and Chief Executive Officer of the Company. In connection with this appointment, the size of the Board was increased to nine, and Mr. Sibold was also appointed a member of the Board. On Mr. Sibold's start date, he assumed the duties and responsibilities of the Company's principal executive officer from Paul Friedman, M.D., who previously served as the Chief Executive Officer since July of 2016. Dr. Friedman continues to serve on the Board as a director of the Company.

Additionally in September 2023, the U.S. Food and Drug Administration (the "FDA") informed Madrigal that it accepted for review our New Drug Application ("NDA") for resmetirom for the treatment of adult patients with NASH with liver fibrosis and granted a Priority Review designation. The FDA has assigned a Prescription Drug User Fee Act ("PDUFA") date of March 14, 2024, the target date by which the FDA intends to complete its review and take action on the NDA. The FDA noted in its September 2023 correspondence that it is not currently planning to hold an advisory committee meeting to discuss our application.

In April 2023, Madrigal announced that resmetirom has received Breakthrough Therapy designation from the FDA for the treatment of patients with NASH with liver fibrosis. Breakthrough Therapy designation is a process intended to expedite the development and review of drugs for serious or life-threatening conditions. The criteria for breakthrough therapy designation require preliminary clinical evidence that demonstrates the drug may have substantial improvement on at least one clinically significant endpoint over available therapy, or over placebo if there is no available therapy. A drug that receives Breakthrough Therapy designation is eligible for more intensive guidance on an efficient drug development program and organizational commitment involving senior managers from FDA.

Also in April 2023, Madrigal announced that the outcomes portion of the Phase 3 MAESTRO-NASH biopsy trial has completed enrollment. Enrollment of the MAESTRO-NASH study was closed at approximately 1,750 patients based on the enrollment target of the 54-month long-term clinical outcome portion of the study.

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 candidate, resmetirom. 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 2021, 2022, and 2023 and we expect that our research and development expenses may increase 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 research, results of ongoing and future clinical trials, potential 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 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 generally accepted accounting principles in the United States. 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 and stock-based compensation 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 our preclinical and clinical programs. In particular, we have 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 our estimates. Our historical estimates for research and development costs have not been materially different from the actual costs.

Stock-Based Compensation

We recognize stock-based compensation expense based on the grant date fair value of stock options, restricted stock units, and other stock-based compensation awards granted to employees, officers, directors, and consultants. We use the Black-Scholes option pricing model to determine the grant date fair value of stock options 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. We use the simplified method for determining the expected lives of options. Expected volatility is based upon an industry estimate or blended rate including our 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. We estimate the forfeiture rate based on historical data. This analysis is re-evaluated at least annually and the forfeiture rate is adjusted as necessary.

For other stock-based compensation awards granted to employees and directors that vest based on market conditions, such as the trading price of our common stock achieving or exceeding certain price targets, we use a Monte Carlo simulation model to estimate the grant date fair value and recognize stock compensation expense over the derived service period. The Monte Carlo simulation model requires key inputs that are subject to uncertainty for risk-free interest rate, dividend yield, volatility, and expected life.

The assumptions used in computing the fair value of equity awards reflect our best estimates but involve uncertainties related to market and other conditions. Changes in any of these assumptions may materially affect the fair value of awards granted and the amount of stock-based compensation recognized.

Certain of the employee stock options we grant are structured to qualify as incentive stock options (ISOs). Under current tax regulations, we do 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 we may receive a tax deduction. We do 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. We have not recognized any income tax benefit for its share-based compensation arrangements due to the fact that we do not believe it is more likely than not we will realize the related deferred tax assets.

Results of Operations

Comparison of the Years Ended December 31, 2023 and 2022

Revenue

We did not generate any revenue during the years ended December 31, 2023 and 2022, respectively.

Operating Expenses

The following table provides comparative results of our operating expenses for the years ended December 31, 2023 and 2022 (in thousands):

	Year Ended December 31,		Increase / (Decrease)	
	2023	2022	$	%
Research and Development Expenses	$ 272,350	$ 245,441	26,909	11 %
General and Administrative Expenses	108,146	48,130	60,016	125 %
Interest (Income)	(19,578)	(2,185)	17,393	796 %
Interest Expense	12,712	3,964	8,748	221 %
	$ 373,630	$ 295,350	78,280	27 %

Research and Development Expense

The following represents our research and development expenses for the years ended December 31, 2023 and 2022 (in thousands):

	Year Ended December 31,		Increase / (Decrease)	
	2023	2022	$	%
Personnel and Internal Expense	$ 56,824	$ 39,121	17,703	45 %
External Expense	215,526	206,320	9,206	4 %
Total	$ 272,350	$ 245,441	26,909	11 %

Our research and development expenses were $272.4 million for the year ended December 31, 2023 compared to $245.4 million for the year ended December 31, 2022. Research and development expenses increased by $26.9 million in 2023 due primarily to a scale up of manufacturing activities, an increase in headcount, and an increase in stock compensation expense.

General and Administrative Expense

Our general and administrative expenses were $108.1 million for the year ended December 31, 2023 compared to $48.1 million for the year ended December 31, 2022. General and administrative expenses increased by $60.0 million in 2023 due primarily to increases in commercial preparation activities, including a corresponding increase in headcount, and an increase in stock compensation expense. We believe our general and administrative expenses will increase over time as we prepare for commercialization and expand our operating activities, which will result in an increase in our headcount, consulting services, and related overhead needed to support those efforts.

Interest Income

Our interest income was $19.6 million for the year ended December 31, 2023 compared to $2.2 million for the year ended December 31, 2022. The increase in interest income was due primarily to a higher average principal balance in our investment account in 2023, along with increased interest rates in 2023.

Interest Expense

Our interest expense was $12.7 million for the year ended December 31, 2023, compared to $4.0 million for the year ended December 31, 2022. The increase in interest expense was primarily a result of higher outstanding principal balances during the period under the Loan Facility with Hercules.

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

The following represents our research and development expenses for the years ended December 31, 2022 and 2021 (in thousands):

	Year Ended December 31,		Increase / (Decrease)	
	2022	2021	$	%
Personnel and Internal Expense	$ 39,121	$ 26,232	12,889	49 %
External Expense	206,320	178,932	27,388	15 %
Total	$ 245,441	$ 205,164	40,277	20 %

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.

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 a corresponding increase in headcount, and an increase in stock compensation expense.

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 $0.0 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.

Liquidity and Capital Resources

Since inception, we have incurred significant net losses and we have funded our operations primarily through the issuance of shares of our common stock, shares of our convertible preferred stock, issuances of pre-funded warrants, borrowings under the Loan Facility with Hercules, the issuance of convertible debt and the proceeds from the merger with Synta Pharmaceuticals Corp. Our most significant use of capital pertains to salaries and benefits for our employees, including commercial, clinical, scientific, operational, financial and management personnel, along with manufacturing costs and commercialization costs to support a potential U.S. approval.

As of December 31, 2023, we had cash, cash equivalents and marketable securities totaling $634.1 million compared to $358.8 million as of December 31, 2022, with the increase primarily attributable to our October 2023 public offering which provided $472.0 million net cash proceeds, partially offset by funding of operations. 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 preparation for commercialization, we believe our available cash resources are 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 may 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, if needed, 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, as well as commercial preparation investments, 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.

At-the-Market Sales Agreement

On May 9, 2023, we entered into Amendment No. 1 (the "Sales Agreement Amendment") to the June 2021 Sales Agreement (the "2021 Sales Agreement") with Cowen, which provided for up to an additional $200.0 million in the amount of common stock that can be issued and sold by us from time to time through or to Cowen under the 2021 Sales Agreement, acting as agent or principal.

Sales of our common stock, if any, under the Sales Agreement will be made by any method that is deemed to be an "at the market" offering as defined in Rule 415(a)(4) of the Securities Act of 1933, as amended. We have no obligation to sell any common stock and may at any time suspend offers under the Sales Agreement or terminate the Sales Agreement pursuant to its terms.

During the three months ended December 31, 2023, under the Sales Agreement Amendment, we sold no shares. During the year ended December 31, 2023, and in total under the Sales Agreement Amendment, we sold 98,101 shares for an aggregate of $25.2 million in gross proceeds, with net proceeds of approximately $24.5 million after deducting commissions and other transaction costs. All shares were sold pursuant to our effective Registration Statement and the prospectus supplement relating thereto. As of December 31, 2023, $174.8 million remained reserved and available for sale under the 2023 Sales Agreement Amendment and our related prospectus supplement.

Loan Facility

In May 2022 we entered into the $250.0 million Loan Facility (the "Loan Facility") with Hercules Capital, Inc. ("Hercules"). On February 3, 2023, we entered into the First Amendment (the "Amendment") to the Loan Facility (as amended, the "Amended Loan Facility"). Under the terms of the Loan Facility, the first $50.0 million tranche ("Tranche 1") was drawn at closing. Under the Amended Loan Facility, $65.0 million was drawn in 2023 under the second tranche ("Tranche 2"). The third tranche ("Tranche 3") of $75.0 million is available, subject to us obtaining a certain FDA approval for resmetirom. The fourth tranche ("Tranche 4") of $60.0 million is available subject to Hercules' sole discretion. In connection with Tranche 1, in 2022 we issued Hercules warrants to purchase 14,899 shares of our common stock, which had a Black-Scholes value of $0.6 million. In connection with Tranche 2, in 2023 we issued to Hercules warrants to purchase an aggregate of 4,555 shares of common stock, which had a Black-Scholes value of $0.9 million.

The Loan Facility had a minimum interest rate of 7.45% and adjusted with changes in the prime rate. 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%. We 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 our

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.

The Loan Facility includes affirmative and restrictive financial covenants which commenced 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 we achieve 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: our failure to make required payments or maintain compliance with covenants under the Loan Facility; our breach of certain representations or default under certain obligations outside the Loan Facility; insolvency, attachment or judgment events affecting us; and any circumstance which has occurred or could reasonably be expected to have a material adverse effect on us, 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, 2023, the outstanding principal under the Loan Facility was $115.0 million. The interest rate as of December 31, 2023 was 10.95%. As of December 31, 2023, we were in compliance with all loan covenants and provisions.

2023 Public Offering

On September 28, 2023, we entered into an Underwriting Agreement with Goldman Sachs & Co. LLC, as representative of the several underwriters named therein, pursuant to which we sold to the underwriters in an underwritten public offering (the "Offering"): (i) 1,248,098 shares of common stock at a public offering price of $151.69 per share, and (ii) pre-funded warrants (the "Pre-Funded Warrants") to purchase 2,048,098 shares of common stock at a public offering price of $151.6899 per Pre-Funded Warrant, which represents the per share public offering price for the common stock less a $0.0001 per share exercise price for each such Pre-Funded Warrant. The Offering closed on October 3, 2023.

The gross proceeds of the Offering was $500.0 million, and we received net proceeds, after deducting the underwriting discount and commissions and other estimated offering expenses payable by us, of approximately $472.0 million. We intend to use the net proceeds from the Offering for our clinical and commercial activities in preparation for a potential launch of resmetirom in the U.S. and for general corporate purposes, including, without limitation, research and development expenditures, clinical trial expenditures, manufacture and supply of drug substance and drug products, potential acquisitions or licensing of new technologies, capital expenditures and working capital.

The Pre-Funded Warrants are exercisable at any time after the date of issuance. A holder of Pre-Funded Warrants may not exercise the warrant if the holder, together with its affiliates, would beneficially own more than 9.99% of the number of shares of common stock outstanding immediately after giving effect to such exercise. A holder of Pre-Funded Warrants may increase or decrease this percentage, but not in excess of 19.99%, by providing at least 61 days prior notice to us.

Cash Flows

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

	Year Ended December 31,		
	2023	2022	2021
Net cash used in operating activities	$ (324,230)	$ (224,857)	$ (183,917)
Net cash provided by (used in) investing activities	(502,520)	206,686	(5,055)
Net cash provided by financing activities	595,116	313,451	171,237
Net increase (decrease) in cash and cash equivalents	$ (231,634)	$ 295,280	$ (17,735)

Operating Activities

Net cash used in operating activities was $324.2 million, $224.9 million, and $183.9 million for the years ended December 31, 2023, 2022 and 2021, 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, 2023 increased from prior years predominately due to the build out of our commercial operations in anticipation of our potential commercial launch.

Investing Activities

Net cash used in investing activities was $502.5 million for the year ended December 31, 2023 and consisted primarily of $834.4 million of purchases of marketable securities for our investment portfolio, partially offset by $333.4 million from sales and maturities of marketable securities from our investment portfolio.

Net cash used in 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.

Financing Activities

Net cash provided by financing activities was $595.1 million for the year ended December 31, 2023 and consisted primarily of $472.0 million in proceeds from our October 2023 public offering, in addition to $65.0 million in borrowings under the Loan Facility, $34.0 million from proceeds from the exercise of common stock options, and $24.5 million from sales of our common stock under the 2023 Sales Agreement, partially offset by $0.4 million of loan issuance costs.

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 a registered direct offering of Series B Convertible Preferred Stock and common stock 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.

Contractual Obligations and Commercial Commitments

As of December 31, 2023, 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	1,861	937	924	—	
Total contractual Obligations	1,861	937	924	—	

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

In August 2023, we entered into the Fifth Amendment to our Office Lease (the "Lease Amendment"). The Lease Amendment extends the term of the lease through November 2026. As a result of the Lease Amendment, an incremental $1.6 million ROU asset and lease liabilities were recorded during the year ended December 31, 2023.

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, 2023, we had drawn $115.0 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, 2023, 2022 or 2021.

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, 2023.

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, 2023. 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, 2023.

PricewaterhouseCoopers LLP, an independent registered public accounting firm, has audited the effectiveness of our internal control over financial reporting as of December 31, 2023, 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 year ended December 31, 2023 that have materially affected, or are reasonably likely to materially affect our internal control over financial reporting.

Item 9B. Other Information.

Director and Executive Officer Adoption of 10b5-1 Plans

Our Section 16 officers and directors may enter into plans or arrangements for the purchase or sale of our securities that are intended to satisfy the affirmative defense conditions of Rule 10b5-1(c) of the Exchange Act. Such plans and arrangements must comply in all respects with our insider trading policies, including our policy governing entry into and operation of 10b5-1 plans and arrangements.

During the quarter ended December 31, 2023: the following Section 16 officers and directors adopted Rule 10b5-1 trading arrangements (as defined in Item 408 of Regulation S-K of the Exchange Act); and no plans were modified or terminated. All plans adopted covered sales of Madrigal common stock (including sales of Madrigal common stock following exercise of stock options).

Name of Director or Section 16 Officer	Title of Director or Section 16 Officer	Date of Adoption, Modification, or Termination	Duration of the Plan	Aggregate Number of Shares of Common Stock that may be Sold under the Plan
Becky Taub, MD	President of R&D, CMO and Director	11/27/2023	April 3, 2025	76,564
Kenneth Bate	Director	11/16/2023	June 27, 2024	32,489
James Daly	Director	11/16/2023	June 27, 2024	32,489
Paul Friedman, MD	Director	11/27/2023	April 3, 2025	100,000
Richard Levy, MD	Director	11/30/2023	June 16, 2025	26,000

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 2024 Proxy Statement, no later than April 29, 2024, and certain information to be included in the 2024 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 2024 Proxy Statement (excluding the information contained under the heading "Executive Officer and Director Compensation--Pay Versus Performance").

Item 11. Executive Compensation.

The information required by this item regarding executive compensation is incorporated by reference in our 2024 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 2024 Proxy Statement. In addition, information about our equity compensation plans is incorporated herein by reference to our 2024 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 2024 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 2024 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 Amendment to Restated Certificate of Incorporation of Madrigal Pharmaceuticals, Inc., as filed on June 16, 2023 with the Secretary of State of the State of Delaware		Form 8-K (Exhibit 3.1)	6/20/2023	001-33277
3.3	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
3.4	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
3.5	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	Form of Pre-Funded Warrant of the Registrant		Form 8-K (Exhibit 4.1)	10/2/2023	001-33277
4.4	Description of Securities of the Registrant		Form 10-K (Exhibit 4.3)	2/23/2023	001-33277
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
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

Exhibit Number	Exhibit Description	Filed Herewith	Incorporated by Reference herein from Form or Schedule	Filing Date	SEC File / Registration Number
10.5	Amendment No. 1 to Sales Agreement, dated May 9, 2023, by and between Madrigal Pharmaceuticals, Inc. and Cowen and Company, LLC.		Form 8-K (Exhibit 1.1)	5/9/2023	001-33277
10.6	Registration Rights Agreement, dated August 7, 2023, by and among Madrigal Pharmaceuticals, Inc., 667, L.P. and Baker Brothers Life Sciences, L.P.		Form 10-Q (Exhibit 10.2)	8/8/2023	001-33277
Debt Agreements					
10.7†	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					
10.8	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					
10.9*	Amended 2015 Stock Plan		Definitive Proxy Statement (Annex A)	4/30/2021	001-33277
10.10*	Form of Incentive Stock Option Agreement under Amended 2015 Stock Plan.		Form 10-K (Exhibit 10.10)	3/31/2017	001-33277
10.11*	Form of Nonqualified Stock Option Agreement under Amended 2015 Stock Plan.		Form 10-K (Exhibit 10.11)	3/31/2017	001-33277
10.12*	Form of Nonqualified Stock Option Agreement for Directors under Amended 2015 Stock Plan (pre-2023).		Form 10-K (Exhibit 10.13)	3/31/2017	001-33277
10.13*	Non-Employee Director Equity Compensation Policy		Form 10-Q (Exhibit 10.1)	5/6/2021	001-33277
10.14*	Form of RSU Agreement for Directors under Amended 2015 Stock Plan		Form 10-Q (Exhibit 10.3)	8/8/2023	001-33277
10.15*	Form of RSU Agreement for Executive Officers (2023) under Amended 2015 Stock Plan		Form 10-Q (Exhibit 10.4)	8/8/2023	001-33277
10.16*	Form of RSU Agreement for Employees under Amended 2015 Stock Plan		Form 10-Q (Exhibit 10.5)	8/8/2023	001-33277
10.17*†	2023 Inducement Plan		Form S-8	9/11/2023	333-27445
10.18*†	Form of Stock Option Agreement under 2023 Inducement Plan		Form S-8	9/11/2023	333-27445
10.19*†	Form of Restricted Stock Unit Agreement under 2023 Inducement Plan		Form S-8	9/11/2023	333-27445
Agreements with Executive Officers and Directors					
10.20*	Form of Indemnification Agreement between the Registrant and certain directors and executive officers.	X			
10.21*	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
10.22*†	Letter Agreement (including agreements attached as exhibits thereto), dated September 7, 2023, by and between Madrigal Pharmaceuticals, Inc. and William J. Sibold		Form 8-K (Exhibit 10.1)	9/13/2023	001-33277
21.1	List of Subsidiaries.		Form 10-K (Exhibit 21.1)	2/23/2023	001-33277
23.1	Consent of PricewaterhouseCoopers LLP, Independent Registered Public Accounting Firm.	X			

Exhibit Number	Exhibit Description	Filed Herewith	Incorporated by Reference herein from Form or Schedule	Filing Date	SEC File / Registration Number
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			
97.1	Incentive Compensation Recovery Policy	X			
101.INS	Inline XBRL Instance Document.	X			
101.SCH	Inline XBRL Taxonomy Extension Schema Document.	X			
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 28, 2024

By: /s/ WILLIAM J. SIBOLD
William J. Sibold
President and 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 William J. Sibold, 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/ WILLIAM J. SIBOLD William J. Sibold	President and Chief Executive Officer (Principal Executive Officer)	February 28, 2024
/s/ ALEX G. HOWARTH Alex G. Howarth	Chief Financial Officer (Principal Accounting and Financial Officer)	February 28, 2024
/s/ JULIAN C. BAKER Julian C. Baker	Director	February 28, 2024
/s/ REBECCA TAUB, M.D. Rebecca Taub, M.D.	Director	February 28, 2024
/s/ FRED B. CRAVES, PH.D. Fred B. Craves, Ph.D.	Director	February 28, 2024
/s/ KENNETH M. BATE Kenneth M. Bate	Director	February 28, 2024
/s/ PAUL A. FRIEDMAN, M.D. Paul A. Friedman, M.D.	Director	February 28, 2024
/s/ RAYMOND CHEONG Raymond Cheong	Director	February 28, 2024

Signatures	Title	Date
/s/ RICHARD S. LEVY, M.D. Richard S. Levy, M.D.	Director	February 28, 2024
/s/ JAMES M. DALY James M. Daly	Director	February 28, 2024

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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, 2023 and 2022, 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, 2023, 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, 2023, 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, 2023 and 2022, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2023 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, 2023, 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 may 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 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, 2023 were $272.4 million and research and development costs accrued were $50.7 million as of December 31, 2023.

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 research and development costs to accrue in the reporting period; and (ii) the high degree of auditor judgment, subjectivity and effort in performing procedures and evaluating management's significant assumptions related to using contracted site and patient costs applied to the number of patients screened for and enrolled in the trials to estimate costs incurred that have not been invoiced.

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 invoices and assessing whether there were significant changes in contracts, 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 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 28, 2024

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, 2023	December 31, 2022
Assets		
Current assets:		
Cash and cash equivalents	$ 99,915	$ 331,
Marketable securities	534,216	27,
Prepaid expenses and other current assets	3,150	2,
Total current assets	637,281	361,
Property and equipment, net	1,553	
Right-of-use asset	1,713	
Total assets	$ 640,547	$ 362,
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 28,041	$ 23,
Accrued expenses	89,980	91,
Lease liability	527	
Total current liabilities	118,548	115,
Long term liabilities:		
Loan payable, net of discount	115,480	49,
Lease liability	1,186	
Total long term liabilities	116,666	49,
Total liabilities	235,214	165,
Stockholders' equity:		
Preferred stock, par value $0.0001 per share authorized: 5,000,000 shares at December 31, 2023 and December 31, 2022; 2,369,797 and 2,369,797 shares issued and outstanding at December 31, 2023 and December 31, 2022, respectively	—	
Common stock, par value $0.0001 per share authorized: 200,000,000 at December 31, 2023 and December 31, 2022; 19,875,427 and 18,102,523 shares issued and outstanding at December 31, 2023 and December 31, 2022, respectively	2	
Additional paid-in-capital	1,741,153	1,160,
Accumulated other comprehensive income (loss)	468	
Accumulated deficit	(1,336,290)	(962,
Total stockholders' equity	405,333	197,
Total liabilities and stockholders' equity	$ 640,547	$ 362,

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,		
	2023	**2022**	**2021**
Revenues:			
Total revenues	$ —	$ —	$
Operating expenses:			
Research and development	272,350	245,441	205,
General and administrative	108,146	48,130	37,
Total operating expenses	380,496	293,571	242,
Loss from operations	(380,496)	(293,571)	(242,
Interest income	19,578	2,185	
Interest expense	(12,712)	(3,964)	
Other income	—	—	
Net loss	$ (373,630)	$ (295,350)	$ (241,
Net loss per common share:			
Basic and diluted net loss per common share	$ (19.99)	$ (17.23)	$ (14
Basic and diluted weighted average number of common shares outstanding	18,687,774	17,137,201	16,535

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,		
	2023	2022	2021
Net Loss	$ (373,630)	$ (295,350)	$ (241,3
Other comprehensive income (loss):			
Unrealized gain (loss) on available-for-sale securities	500	48	(
Comprehensive loss	$ (373,130)	$ (295,302)	$ (241,9

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, 2020	1,969,797	$ —	15,508,146	$ 2	$ 665,385	$ 47	$ (425,464)	$ 23
Issuance of common shares in equity offering, excluding to related parties, net of transaction costs	—	—	1,584,169	—	170,207	—	—	17
Sale of common shares to related parties and exercise of common stock options, net of transaction costs	—	—	11,080	—	1,030	—	—	
Compensation expense related to stock options for services	—	—	—	—	26,873	—	—	2
Unrealized loss on marketable securities	—	—	—	—	—	(127)	—	
Net loss	—	—	—	—	—	—	(241,846)	(24
Balance at December 31, 2021	1,969,797	$ —	17,103,395	$ 2	$ 863,495	$ (80)	$ (667,310)	$ 19
Issuance of common and preferred shares in equity offerings, excluding to related parties, net of transaction costs	400,000	—	783,344	—	255,382	—	—	25
Sale of common shares to related parties and exercise of common stock options, net of transaction costs	—	—	215,784	—	8,955	—	—	
Compensation expense related to stock options for services	—	—	—	—	31,625	—	—	3
Unrealized gain on marketable securities	—	—	—	—	—	48	—	
Hercules warrant	—	—	—	—	622	—	—	
Net loss	—	—	—	—	—	—	(295,350)	(29
Balance at December 31, 2022	2,369,797	$ —	18,102,523	$ 2	$ 1,160,079	$ (32)	$ (962,660)	$ 19
Issuance of common and preferred shares in equity offerings, excluding to related parties, net of transaction costs	—	—	1,346,199	—	260,187	—	—	26
Sale of warrants and common shares to related parties and exercise of common stock options, net of transaction costs	—	—	426,705	—	270,292	—	—	27
Compensation expense related to stock options for services	—	—	—	—	49,735	—	—	4
Unrealized gain on marketable securities	—	—	—	—		500	—	
Hercules warrant	—	—	—	—	860	—	—	
Net loss	—	—	—	—	—	—	(373,630)	(37
Balance at December 31, 2023	2,369,797	—	19,875,427	$ 2	$ 1,741,153	$ 468	$ (1,336,290)	$ 40

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,		
	2023	**2022**	**2021**
Cash flows from operating activities:			
Net loss	$ (373,630)	$ (295,350)	$ (241,
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense	49,735	31,625	26,
Depreciation and amortization expense	527	467	
Amortization of debt issuance costs and discount	2,414	797	
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	(555)	(1,257)	(
Accounts payable	4,210	2,451	20,
Accrued expense	(1,481)	36,413	9,
Accrued interest, net of interest received on maturity of investments	(5,450)	(3)	
Net cash used in operating activities	(324,230)	(224,857)	(183,
Cash flows from investing activities:			
Purchases of marketable securities	(834,439)	(143,478)	(394,
Sales and maturities of marketable securities	333,398	350,381	389,
Purchases of property and equipment, net of disposals	(1,479)	(217)	(
Net cash provided by (used in) investing activities	(502,520)	206,686	(5,
Cash flows from financing activities:			
Proceeds from issuances of stock, excluding related parties, net of transaction costs	260,187	255,382	170,
Proceeds from the sale of related party warrants and stock and exercise of common stock options, net of transaction costs	270,292	8,955	1,
Proceeds from issuance of loan payable	65,000	50,000	
Payment of debt issuance costs	(363)	(886)	
Net cash provided by financing activities	595,116	313,451	171,
Net increase (decrease) in cash and cash equivalents	(231,634)	295,280	(17,
Cash and cash equivalents at beginning of period	331,549	36,269	54,
Cash and cash equivalents at end of period	$ 99,915	$ 331,549	$ 36,
Supplemental disclosure of cash flow information:			
Obtaining a right-of-use asset in exchange for a lease liability	$ 1,628	$ 583	$

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 biopharmaceutical company pursuing novel therapeutics for nonalcoholic steatohepatitis ("NASH"), a liver disease with high unmet medical need. The Company's lead candidate, resmetirom, a once-daily, oral, liver-directed thyroid hormone receptor-β ("THR-β") agonist designed to target key underlying causes of NASH, is in registration status following review acceptance by the U.S. Food and Drug Administration (the "FDA") for its New Drug Application ("NDA") in September 2023.

Basis of Presentation

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, 2023, 2022 and 2021, the Company determined it did not have any securities that were other-than-temporarily impaired.

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, 2023, 2022 and 2021, 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, 2023 and 2022, the Company's financial assets valued based on Level 1 inputs consisted of cash and cash equivalents in a money market fund, its financial assets valued based on Level 2 inputs consisted of high-grade corporate and government agency bonds and commercial paper, and it had no financial assets valued based on Level 3 inputs. During the years ended December 31, 2023, 2022 and 2021, the Company did not have any transfers of financials assets between Levels 1 and 2. As of December 31, 2023 and 2022, 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 its drug, and conducted 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 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.

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 $0.9 million, $0.5 million and $0.5 million for the years ended December 31, 2023, 2022 and 2021, respectively.

Stock-Based Compensation

The Company recognizes stock-based compensation expense based on the grant date fair value of stock options, restricted stock units, and other stock-based compensation awards granted to employees, officers, directors, and consultants. Awards that vest as the recipient provides service are expensed on a straight-line basis over the requisite service period.

The Company uses the Black-Scholes option pricing model to determine the grant date fair value of stock options 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.

For other stock-based compensation awards granted to employees and directors that vest based on market conditions, such as the trading price of the Company's common stock achieving or exceeding certain price targets, the Company uses a Monte Carlo simulation model to estimate the grant date fair value and recognize stock compensation expense over the derived service period. The Monte Carlo simulation model requires key inputs for risk-free interest rate, dividend yield, volatility, and expected life.

The assumptions used in computing the fair value of equity awards reflect the Company's best estimates but involve uncertainties related to market and other conditions. Changes in any of these assumptions may materially affect the fair value of awards granted and the amount of stock-based compensation recognized.

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. 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, 2023, 2022 and 2021, diluted net loss per share is the same as basic net loss per share because

the inclusion of weighted average shares of common stock issuable upon the exercise of stock options and warrants or vesting of restricted stock units, 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,		
	2023	2022	2021
Common stock options	2,355,779	2,857,054	2,301,574
Restricted stock units	376,117	—	—
Performance-based restricted stock units	150,000	—	—
Preferred stock	2,369,797	2,369,797	1,969,797
Warrants	2,067,552	14,899	—

Recent Accounting Pronouncements Not Yet Adopted

In November 2023, the Financial Accounting Standards Board (“FASB”) issued ASU 2023-07, Segment Reporting (Topic 280): Improvements to Reportable Segment Disclosures, which enhances the disclosures required for operating segments in the Company's annual and interim consolidated financial statements. The amendments are effective for fiscal years beginning after December 15, 2023, and interim periods beginning after December 15, 2024. Early adoption is permitted. The Company is currently evaluating the impact of ASU 2023-07 on its financial statements.

In December 2023, the FASB issued ASU 2023-09, Income Taxes (Topic 740): Improvements to Income Tax Disclosures, which enhances the disclosures required for income taxes in the Company's annual consolidated financial statements. The amendments are effective for annual periods beginning after December 15, 2024. Early adoption is permitted. The Company is currently evaluating the impact of ASU 2023-09 on its financial statements.

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 $373.6 million for the year ended December 31, 2023, resulting in an accumulated deficit of approximately $1,336.3 million and $962.7 million as of December 31, 2023 and 2022, 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 and debt financings. In October 2023, the Company completed a public offering and received approximately $472.0 million net cash proceeds. The Company believes that its cash, cash equivalents and marketable securities at December 31, 2023 will be sufficient to fund operations past one year from the issuance of these financial statements. To meet its future capital needs, the Company may need 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, if at all, 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 planned commercialization costs, product manufacturing, 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, 2023 and 2022 is as follows (in thousands):

	December 31, 2023			
	Cost	Unrealized gains	Unrealized losses	Fair value
Cash and cash equivalents:				
Cash (Level 1)	$ 2,729	$ —	$ —	$ 2,7
Money market funds (Level 1)	78,555	—	—	78,5
US government and government sponsored entities (Level 1)	14,967	—	—	14,9
Corporate debt securities due within 3 months of date of purchase (Level 2)	3,664	—	—	3,6
Total cash and cash equivalents	99,915	—	—	99,9
Marketable securities:				
Corporate debt securities due within 1 year of date of purchase (Level 2)	382,028	195	(7)	382,2
US government and government sponsored entities due within 1 year of date of purchase (Level 2)	150,743	280	(1)	151,0
Corporate debt securities due within 1 to 2 years of date of purchase (Level 2)	$ 977	$ 1	$ —	$ 9
Total cash, cash equivalents and marketable securities	$ 633,663	$ 476	$ (8)	$ 634,1

	December 31, 2022			
	Cost	Unrealized gains	Unrealized losses	Fair value
Cash and cash equivalents:				
Cash (Level 1)	$ 15,100	$ —	$ —	$ 15,1
Money market funds (Level 1)	316,449	—	—	316,4
Total cash and cash equivalents	331,549	—	—	331,5
Marketable securities:				
Corporate debt securities due within 1 year of date of purchase (Level 2)	27,257	7	(39)	27,2
Total cash, cash equivalents and marketable securities	$ 358,806	$ 7	$ (39)	$ 358,7

5. Accrued Liabilities

Accrued liabilities as of December 31, 2023 and 2022 consisted of the following (in thousands):

	December 31, 2023	December 31, 2022
Contract research organization costs	$ 50,737	$ 53,119
Other clinical study related costs	3,724	6,582
Manufacturing and drug supply	9,705	11,262
Compensation and benefits	17,030	14,864
Professional fees	6,814	4,867
Other	1,970	767
Total accrued liabilities	$ 89,980	$ 91,461

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 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.

On February 3, 2023, the Company entered into the First Amendment (the "Amendment") to the Loan Facility (as amended, the "Amended Loan Facility"). 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. An additional $15.0 million was drawn under Tranche 2 in June of 2023. The remaining $15.0 million available under Tranche 2 was drawn in September of 2023 in accordance with the Amended Loan Facility. 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 $15.0 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 Tranche 2 at the closing of the Amendment, $15.0 million drawn in June of 2023, and $15.0 million drawn in September of 2023, the Company issued to Hercules and affiliates Tranche 2 Warrants to purchase an aggregate of 4,555 shares of common stock, which had a Black-Scholes value of $0.9 million. 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.

The Loan Facility includes affirmative and restrictive financial covenants which commenced 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, 2023, the outstanding principal under the Loan Facility was $115.0 million. The interest rate as of December 31, 2023 was 10.95%. As of December 31, 2023, 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, 2023 are as follows (in thousands):

Period Ending December 31, 2023:	Amount
2024	$ 12,802
2025	79,604
2026	53,387
	$ 145,793
Less amount representing interest	(24,641)
Less unamortized discount	(5,672)
Loans payable, net of discount	$ 115,480

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 Board"). 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.

2023 Public Offering

On September 28, 2023, the Company entered into an Underwriting Agreement with Goldman Sachs & Co. LLC, as representative of the several underwriters named therein, pursuant to which the Company sold to the underwriters in an underwritten public offering (the "2023 Offering"): (i) 1,248,098 shares of common stock at a public offering price of $151.69 per share, and (ii) pre-funded warrants (the "Pre-Funded Warrants") to purchase 2,048,098 shares of common stock at a public offering price of $151.6899 per Pre-Funded Warrant, which represents the per share public offering price

for the common stock less a $0.0001 per share exercise price for each such Pre-Funded Warrant. The 2023 Offering closed on October 3, 2023.

The gross proceeds of the 2023 Offering was $500.0 million, and the Company received net proceeds, after deducting the underwriting discount and commissions and other estimated offering expenses payable by the Company, of approximately $472.0 million. The Company intends to use the net proceeds from the Offering for its clinical and commercial activities in preparation for a potential launch of resmetirom in the U.S. and for general corporate purposes, including, without limitation, research and development expenditures, clinical trial expenditures, manufacture and supply of drug substance and drug products, potential acquisitions or licensing of new technologies, capital expenditures and working capital.

The Pre-Funded Warrants are exercisable at any time after the date of issuance. A holder of Pre-Funded Warrants may not exercise the warrant if the holder, together with its affiliates, would beneficially own more than 9.99% of the number of shares of common stock outstanding immediately after giving effect to such exercise. A holder of Pre-Funded Warrants may increase or decrease this percentage, but not in excess of 19.99%, by providing at least 61 days prior notice to the Company.

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 $200.0 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 "Original 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 Original 2021 Sales Agreement authorized an aggregate offering of up to $200.0 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 Original 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).

In December 2022, the Company sold 738,900 shares under the Original 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 Original 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 on Form S-3 (the

"Registration Statement") and the prospectus supplement relating thereto. As of December 31, 2023, no amounts remained reserved and available for sale under the Original 2021 Sales Agreement and the related prospectus supplement.

In May 2023, the Company amended the 2021 Agreement (the “Sales Agreement Amendment”), with Cowen, pursuant to which the Company may, from time to time, issue and sell an additional $200.0 million in shares of its common stock. The Company is not obligated to make any sales of its common stock under this arrangement. Any shares sold will be sold pursuant to the Registration Statement and prospectus supplement filed pursuant to the Registration Statement. The Sales Agreement Amendment authorizes sales of shares of the Company’s common stock, from time to time, at the Company’s option, through Cowen as its sales agent. Sales of common stock through Cowen may 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, and as described in the prospectus supplement.

During the three months ended December 31, 2023, under the Sales Agreement Amendment, the Company sold no shares. During the year ended December 31, 2023, and in total under the Sales Agreement Amendment, the Company sold 98,101 shares for an aggregate of $25.2 million in gross proceeds, with net proceeds to the Company of approximately $24.5 million after deducting commissions and other transaction costs. All shares were sold pursuant to the Company’s effective Registration Statement and the prospectus supplement relating thereto. As of December 31, 2023, $174.8 million remained reserved and available for sale under the 2023 Sales Agreement Amendment and the Company’s related prospectus supplement.

8. Stock-based Compensation

2015 Stock Plan

The 2015 Stock Plan, as amended (the “2015 Stock Plan”), is our shareholder-approved incentive plan through which equity based grants are awarded. The 2015 Stock Plan provides for the grant of incentive stock options, non-statutory stock options, restricted stock, restricted stock units 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, 2023, 711,054 shares were available for future issuance under the 2015 Stock Plan.

2023 Inducement Plan

In September 2023, the Company adopted the 2023 Inducement Plan (the “Inducement Plan”), pursuant to which the Company may from time to time make equity grants to new employees as a material inducement to their employment. The Inducement Plan was adopted without stockholder approval, pursuant to Nasdaq Listing Rule 5635(c)(4), and is administered by the Compensation Committee of the Board. The Inducement Plan provides for the granting of non-statutory stock options, restricted stock, restricted stock units, performance stock units and other stock-based compensation awards to new employees, but does not allow for the granting of incentive stock options. The terms of the stock options under the Inducement 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 or award is granted. A total of 500,000 shares of the Company’s common stock were reserved for issuance under the Inducement Plan. As of December 31, 2023, 193,392 shares were available for future issuance under the 2023 Inducement Plan.

Stock Options

The following table summarizes stock option activity during the year ended December 31, 2023:

	Shares	Weighted average exercise price	Weighted average remaining contractual life (years)	Aggregate intrinsic value (in thousands)
Outstanding at January 1, 2023	2,857,054	$ 81.78		
Options granted	31,111	190.91		
Options exercised	(460,385)	88.83		
Options cancelled	(72,001)	144.24		
Outstanding at December 31, 2023	2,355,779	$ 79.94	5.51	$ 359,861
Exercisable at December 31, 2023	1,774,976	$ 74.49	4.71	$ 281,400

The total cash received by the Company as a result of stock option exercises was $34.0 million, $9.0 million and $1.0 million for the years ended December 31, 2023, 2022, and 2021. The total intrinsic value of options exercised was $70.4 million $47.3 million and $0.1 million for the years ended December 31, 2023, 2022, and 2021. The weighted-average grant date fair values, based on the Black-Scholes option model, of options granted during the year ended December 31, 2023, 2022 and 2021 was $149.15, $54.68, and $73.29, respectively.

Restricted Stock Units

The Company's 2015 Stock Plan provides for awards of restricted stock units ("RSUs") to employees, officers, directors and consultants to the Company. The Company's Inducement Plan provides for awards of RSUs to new employees. RSUs vest over a period of months or years, or upon the occurrence of certain performance criteria or the attainment of stated goals or events, and are subject to forfeiture if employment or service terminates before vesting.

The following table summarizes RSU activity, excluding performance-based RSUs, during the year ended December 31, 2023:

	Shares	Weighted average grant date fair value
Unvested at January 1, 2023	—	$ —
RSUs granted	398,600	243.81
RSUs vested	(356)	299.98
RSUs forfeited	(22,127)	283.05
Unvested at December 31, 2023	376,117	$ 241.45

Performance-Based Restricted Stock Units

The Company has granted various performance-based restricted stock units ("PSUs") to certain senior leadership. Depending on the terms of the PSUs and the outcome of the pre-established performance criteria, which may include a market and/or performance condition, a recipient may ultimately earn the target number of PSUs granted or a specified multiple thereof at the end of the vesting period.

As of December 31, 2023, the Company granted 50,000 PSUs. The maximum number of PSUs eligible to be earned of 150,000 are outstanding under the Inducement Plan as of December 31, 2023, with a weighted average grant date fair value of $146.37 per unit.

Outstanding Awards

As of December 31, 2023, the Company had restricted stock units, performance stock units, and options outstanding pursuant to which an aggregate of 2,881,896 shares of its common stock may be issued pursuant to the terms of all awards granted under the 2015 Stock Plan and Inducement Plan.

Stock-Based Compensation Expense

Stock-based compensation expense during the years ended December 31, 2023, 2022 and 2021 was as follows (in thousands):

	Year Ended December 31,		
	2023	2022	2021
Stock-based compensation expense by type of award:			
Stock options	$ 30,613	$ 31,625	$ 26,873
Restricted stock units	14,974	—	—
Performance-based restricted stock units	4,148	—	—
Total stock-based compensation expense	$ 49,735	$ 31,625	$ 26,873
Effect of stock-based compensation expense by line item:			
Research and development	$ 20,864	$ 13,876	$ 10,698
General and administrative	28,871	17,749	16,175
Total stock-based compensation expense included in net loss	$ 49,735	$ 31,625	$ 26,873

Unrecognized stock-based compensation expense as of December 31, 2023 was $118.2 million with a weighted average remaining period of 2.66 years.

9. Leases

In 2019, the Company entered into an operating lease for office space, which was renewed and extended in 2020. The Company 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.

In August 2023, The Company entered into the Fifth Amendment to its Office Lease (the “Lease Amendment”). The Lease Amendment extends the term of the lease through November 2026. As a result of the Lease Amendment, an incremental $1.6 million ROU asset and lease liabilities were recorded during the year ended December 31, 2023.

Future minimum payments under the Company’s operating leases related to the ROU asset and lease liability as of December 31, 2023 was as follows (in thousand):

	Operating Leases
2024	937
2025	478
2026	446
Total minimum payments	$ 1,861
Less: imputed interest	(148)
Present value of lease liabilities	$ 1,713

As of December 31, 2023, the weighted average remaining operating lease term was 2.9 years and the weighted average discount rate used to determine the operating lease liabilities was 10.95%. Cash paid related to the lease liability was $1.1 million and $0.7 million for years ended December 31, 2023 and 2022 respectively. Operating lease costs were $1.1 million and $0.8 million for years ended December 31, 2023 and 2022 respectively. Rent, short term and variable leases costs were immaterial during the years ended December 31, 2023, 2022 and 2021.

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. Remaining milestones under the agreement total $8.0 million and are earned by achieving specified objectives related to future regulatory approval in the United States and Europe of resmetirom or a product developed from resmetirom. Furthermore, a tiered single-digit royalty is payable on net sales of resmetirom or a product developed from resmetirom, subject to certain reductions. The Company has not achieved any additional product development or regulatory milestones and had no Licensed Product sales for the years ended December 31, 2023, 2022 and 2021.

In August 2023, The Company entered into the Fifth Amendment to the Office Lease (the "Lease Amendment"). The Lease Amendment extends the term of the lease through November 2026. As a result of the Lease Amendment, an incremental $1.6 million ROU asset and lease liabilities were recorded during the year ended December 31, 2023.

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, 2023, the Company had federal net operating loss ("NOL") carryforwards of approximately $489.0 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 $477.6 million, available to reduce future taxable income, which expire between 2031 and 2042. The Company has unused federal research and development carryforwards of approximately $46.1 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. The net operating losses are estimated to be subject to an annual limitation, of which none are expected to expire before becoming available to reduce future taxable income.

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 $112.0 million for the year ended December 31, 2023. 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, 2023 there were no uncertain positions. The 2019 through 2023 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 2023.

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

	For the years ended December 31,		
	2023	2022	2021
Deferred Tax Liabilities			
Unrealized gains on investments	$ 117	$ —	$ —
Total Deferred Tax Liabilities	$ 117	$ —	$ —
Deferred Tax Assets			
Charitable contributions	$ 37	$ 45	$ 53
Accrued expenses	3,857	2,398	1,857
Intangibles	503	589	783
Stock compensation	33,976	27,226	24,335
Property, plant & equipment	95	106	80
Unrealized loss on investment	—	8	23
Net operating losses	121,552	68,305	47,864
Capitalized R&D	175,145	137,328	112,848
R&D credit	48,074	35,103	23,799
Total deferred tax assets before valuation allowance	383,239	271,108	211,642
Valuation allowance	(383,122)	(271,108)	(211,642)
Total deferred tax assets	117	—	—
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,		
	2023	2022	2021
Tax benefit at U.S. federal statutory rate	$ (78,462)	$ (62,023)	$ (50,788)
Stock based compensation	(8,287)	(7,844)	—
162M limitation	3,183	7,996	22
Other nondeductible expenses	53	16	5
State income taxes benefit before valuation allowance, net of federal benefit	(16,246)	13,090	(19,622)
Increase in domestic valuation allowance	112,606	59,466	79,258
Research and development credit	(12,971)	(10,712)	(9,002)
Other adjustments	124	11	127
Income tax expense (benefit)	$ —	$ —	$ —

12. Quarterly Financial Data (unaudited)

The following tables present a summary of quarterly results of operations for 2023 and 2022 (in thousands, except shares and per share data):

	Three months ended			
	March 31, 2023	June 30, 2023	September 30, 2023	December 31, 2023
Revenues:				
Total revenues	$ —	$ —	$ —	$ —
Operating expenses:				
Research and development	62,154	68,605	70,951	70,640
General and administrative	16,182	17,845	27,583	46,536
Total operating expenses	78,336	86,450	98,534	117,176
Loss from operations	(78,336)	(86,450)	(98,534)	(117,176)
Interest income	3,776	3,551	3,298	8,953
Interest expense	(2,336)	(2,901)	(3,504)	(3,971)
Other income	—	—	—	—
Net loss	$ (76,896)	$ (85,800)	$ (98,740)	$ (112,194)
Net loss per common share:				
Basic and diluted net loss per common share	$ (4.23)	$ (4.69)	$ (5.34)	$ (5.68)
Basic and diluted weighted average number of common shares outstanding	18,187,924	18,310,952	18,476,414	19,760,842

	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

13. Subsequent Event

None.