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, 2024

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 001-38978

FULCRUM THERAPEUTICS, INC.

(Exact name of registrant as specified in its Charter)

Delaware	**47-4839948**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
26 Landsdowne Street Cambridge, Massachusetts	**02139**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (617) 651-8851

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

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common stock, par value $0.001 per share	FULC	Nasdaq Global Market

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

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

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

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

Indicate by check mark whether the registrant has submitted electronically 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, 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 ☒

As of June 30, 2024, the last business day of the registrant's most recently completed second fiscal quarter, the aggregate market value of the registrant's common stock held by non-affiliates of the registrant, based on the closing price of the shares of common stock on the Nasdaq Global Market on June 28, 2024, was approximately $308,714,932.

The number of shares of registrant's common stock outstanding as of February 18, 2025 was 53,979,306.

DOCUMENTS INCORPORATED BY REFERENCE

The registrant intends to file a definitive proxy statement pursuant to Regulation 14A relating to the 2024 Annual Meeting of Stockholders within 120 days of the end of the registrant's fiscal year ended December 31, 2024. Portions of such definitive proxy statement are incorporated by reference into Part III of this Annual Report on Form 10-K to the extent stated herein.

Table of Contents

		Page
PART I		
Item 1.	Business	1
Item 1A.	Risk Factors	35
Item 1B.	Unresolved Staff Comments	77
Item 1C.	Cybersecurity	77
Item 2.	Properties	77
Item 3.	Legal Proceedings	77
Item 4.	Mine Safety Disclosures	78
PART II		
Item 5.	Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities	79
Item 6.	Reserved	79
Item 7.	Management's Discussion and Analysis of Financial Condition and Results of Operations	80
Item 7A.	Quantitative and Qualitative Disclosures About Market Risk	91
Item 8.	Financial Statements and Supplementary Data	91
Item 9.	Changes in and Disagreements With Accountants on Accounting and Financial Disclosure	91
Item 9A.	Controls and Procedures	91
Item 9B.	Other Information	92
Item 9C.	Disclosure Regarding Foreign Jurisdictions that Prevent Inspections	92
PART III		
Item 10.	Directors, Executive Officers and Corporate Governance	93
Item 11.	Executive Compensation	93
Item 12.	Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters	93
Item 13.	Certain Relationships and Related Transactions, and Director Independence	93
Item 14.	Principal Accountant Fees and Services	93
PART IV		
Item 15.	Exhibits and Financial Statement Schedules	94
Item 16.	Form 10-K Summary	94

In this Annual Report on Form 10-K, unless otherwise stated or as the context otherwise requires, references to "Fulcrum," "Fulcrum Therapeutics," "the Company," "we," "us," "our" and similar references refer to Fulcrum Therapeutics, Inc. together with its consolidated subsidiary. The Fulcrum Therapeutics logo and other trademarks or service marks of Fulcrum Therapeutics, Inc. appearing in this Annual Report on Form 10-K are the property of Fulcrum Therapeutics, Inc. This Annual Report on Form 10-K also contains registered marks, trademarks and trade names of other companies. All other trademarks, registered marks and trade names appearing herein are the property of their respective holders.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements, which reflect our current views with respect to, among other things, our operations and financial performance. All statements other than statements of historical facts contained in this Annual Report on Form 10-K, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans, objectives of management and expected market growth are forward-looking statements. The words "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "might," "outlook," "plan," "potential," "predict," "project," "should," "target," "would," and the negative version of these words and other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words and include, among other statements, express or implied statements regarding:

- our ongoing clinical trial of pociredir, including the effects of the revised inclusion and exclusion criteria on our trial of pociredir;
- the impact of our organizational streamlining and realignment of resources, including anticipated savings, as well as our cash runway;
- the timing of and our ability to submit applications for, and obtain and maintain regulatory approvals for pociredir and any other product candidates;
- our expectations regarding our ability to fund our operating expenses and capital expenditure requirements with our cash, cash equivalents, and marketable securities;
- the initiation, timing, progress and results of our current and future preclinical studies and clinical trials (including planned investigational new drug, or IND, application filings) and our research and development programs, including novel therapeutic agents for the potential treatment of inherited aplastic anemias, such as Diamond-Blackfan anemia, or DBA, Shwachman-Diamond syndrome, and Fanconi anemia, and other discovery programs;
- our plans to develop and, if approved, subsequently commercialize pociredir and any other product candidates, including in combination with other drugs and therapies;
- the potential advantages of our product candidates;
- the rate and degree of market acceptance and clinical utility of our products, if our product candidates are approved;
- our estimates regarding the potential market opportunity for our product candidates;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the initiation, timing, progress and results of our drug target discovery screening programs;
- our intellectual property position;
- the progress and results of our collaboration agreement with MyoKardia, Inc., or MyoKardia, a wholly-owned subsidiary of Bristol-Myers Squibb Company, or under our exclusive global license agreement with CAMP4 Therapeutics Corp., or CAMP4;
- our ability to identify, in-license, acquire or develop additional products, product candidates or technologies with significant commercial potential that are consistent with our commercial objectives;
- our estimates regarding expenses, future revenue, timing of any future revenue, capital requirements and needs for additional financing;
- the impact of government laws and regulations, including uncertainty resulting from recent change in administration and shift in government policy and evolving regulatory environment;
- our competitive position;
- developments relating to our competitors and our industry;
- our ability to maintain and establish collaborations, license agreements or obtain additional funding; and
- the impact of global pandemics or other geopolitical events on our business and operations, including our clinical trials and development plans, as well as our future financial results.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Such forward-looking statements are subject to various risks and uncertainties. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in the "Risk Factors" section, that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, collaborations, joint ventures or investments we may make or enter into.

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

This Annual Report on Form 10-K includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties as well as our own estimates of potential market opportunities. All of the market data used in this Annual Report on Form 10-K involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. Our estimates of the potential market opportunities for our product candidates include several key assumptions based on our industry knowledge, industry publications, third-party research and other surveys, which may be based on a small sample size and may fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, no independent source has verified such assumptions.

SUMMARY RISK FACTORS

Our business is subject to a number of risks that if realized could materially affect our business, financial condition, results of operations, cash flows and access to liquidity. These risks are discussed more fully in the “Risk Factors” section of this Annual Report on Form 10-K. Our principal risks include the following:

- We have incurred significant losses since our inception. Our net loss was $9.7 million for the year ended December 31, 2024 and $97.3 million for the year ended December 31, 2023. We expect to incur losses over the next several years and may never achieve or maintain profitability. As of December 31, 2024, we had an accumulated deficit of $519.4 million.
- We will need substantial additional funding. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts. We expect to devote substantial financial resources to our ongoing and planned activities, particularly as we continue our clinical trial of pociredir and continue research and development and initiate additional clinical trials of, and seek regulatory approval for, pociredir and other product candidates.
- We are early in our development efforts, and we only have one product candidate in clinical trials. If we are unable to commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed.
- Clinical drug development involves a lengthy and expensive process, with an uncertain outcome. The results of preclinical studies and early clinical trials may not be predictive of future results. We may incur additional costs or experience further delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.
- Because we are developing some of our product candidates for the treatment of diseases in which there is limited clinical experience and, in some cases, using new endpoints or methodologies, the U.S. Food and Drug Administration, or FDA, or other regulatory authorities may not consider the endpoints of our clinical trials to predict or provide clinically meaningful results.
- If serious adverse events or unacceptable side effects are identified during the development of our product candidates, including others’ product candidates in the same class of drugs, we may need to abandon or limit our development of some of our product candidates.

•We may not be successful in our efforts to use our discovery approach to build a pipeline of product candidates, or to in-license or acquire additional product candidates.

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

•We rely, and expect to continue to rely, on contract manufacturing organizations, or CMOs, to manufacture our product candidates. If we are unable to enter into such arrangements as expected or if such organizations do not meet our supply requirements, development and/or commercialization of our product candidates may be delayed.

•We rely, and expect to continue to rely, on third parties to conduct our clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials, which may harm our business.

•We have entered into, and may in the future enter into, collaborations and license agreements with third parties for the discovery, development or commercialization of product candidates. If our collaborations are not successful or we are not able to develop product candidates that we license-in, we may not be able to capitalize on the market potential of these product candidates and our business could be adversely affected.

•If we are unable to obtain, maintain, enforce and protect patent protection for our technology and product candidates or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully develop and commercialize our technology and product candidates may be adversely affected.

•If we fail to comply with our obligations in our intellectual property licenses and funding arrangements with third parties, or otherwise experience disruptions to our business relationships with our licensors, we could lose intellectual property rights that are important to our business.

•Adverse developments affecting the financial services industry, such as actual events or concerns involving liquidity, defaults or non-performance by financial institutions or transactional counterparties, could adversely affect our current and projected business operations and financial condition and results of operations.

•Our business was negatively impacted by the COVID-19 pandemic and may in the future be impacted by any future pandemics, as well as other geopolitical events that can impact our clinical trials or the supply chain, such as the Russian invasion of Ukraine or hostilities in Israel, Lebanon, and the Gaza Strip, or changes in U.S. economic policy announced by the current administration. These events may adversely impact the U.S. economy and/or economies worldwide, which could result in adverse effects on our business and operations.

PART I

Item 1. Business.

Overview

We are a clinical-stage biopharmaceutical company focused on developing small molecules to improve the lives of patients with genetically defined rare diseases in areas of high unmet medical need. Our clinical-stage product candidate, pociredir, is being developed for the potential treatment of sickle cell disease, or SCD.

In January 2023, we announced interim data from our Phase 1b clinical trial of pociredir in SCD. We completed enrollment in the 6 mg and 2 mg dose cohorts, and do not plan to enroll additional subjects in these cohorts. Although we commenced enrollment in the 12 mg dose cohort, in February 2023 the FDA placed a full clinical hold on the IND application for pociredir for SCD, which was lifted in August 2023. Following the clinical hold, we amended the protocol to revise the inclusion and exclusion criteria for the Phase 1b clinical trial to target subjects with higher disease severity. We reinitiated the Phase 1b clinical trial at the 12 mg once daily dose level in the fourth quarter of 2023, with that cohort expected to enroll approximately 10 subjects, to be followed by an additional cohort of approximately 10 subjects at the 20 mg once daily dose level. Subjects are evaluated over a 12-week treatment period. We have enrolled 10 patients in the 12 mg dose cohort, and we expect to provide clinical data from the 12 mg dose cohort in mid-2025 and from the 20 mg dose cohort by the end of 2025.

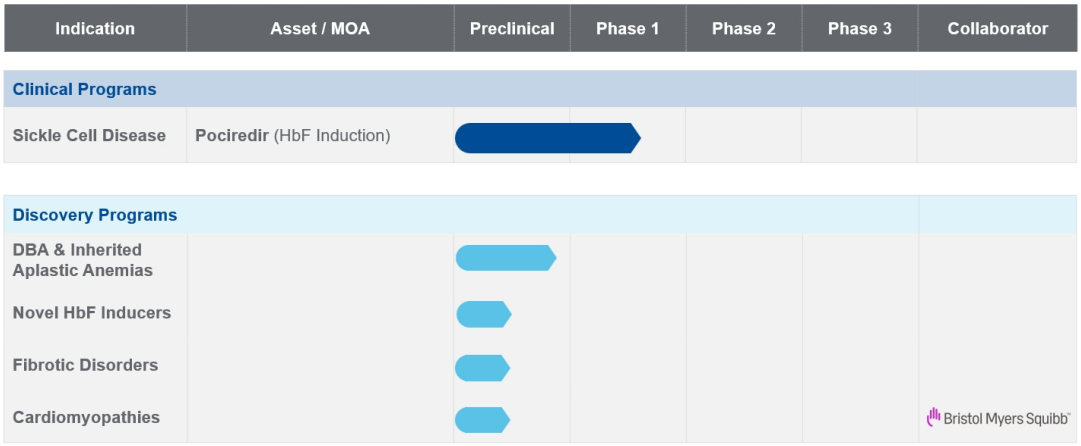
In September 2024, we announced topline results from our Phase 3 REACH clinical trial of losmapimod in facioscapulohumeral muscular dystrophy, or FSHD. The Phase 3 REACH trial did not achieve its primary endpoint of change from baseline in relative surface area with losmapimod compared to placebo. In addition, secondary endpoints did not achieve nominal statistical significance. The safety and tolerability profile of losmapimod was consistent with previously reported studies. Based on the results of the REACH trial, we have suspended future development of losmapimod. We plan to present the results from the Phase 3 REACH trial on March 19, 2025 at the 2025 MDA Conference being held in Dallas, Texas.

In September 2024, we also announced a strategic plan to reprioritize research and development activities and are now focused on advancing pociredir for the treatment of SCD, novel therapeutic agents for the potential treatment of inherited aplastic anemias, such as DBA, Shwachman-Diamond syndrome, and Fanconi anemia, and our other discovery programs. The plan reduced our workforce from 80 to 51 full-time employees, including a reduction of positions across both research and development and general and administrative functions. We estimate that this restructuring will result in annual operating expense savings of approximately $10.0 million beginning in the first quarter of 2025.

In addition to our product candidates, we developed a discovery approach that we employ to systematically identify and validate cellular drug targets that can potentially modulate gene expression to treat known root causes of genetically defined rare diseases. Our discovery approach led to the identification of pociredir for SCD, as well as other drug candidates.

Our Pipeline

Using our discovery approach, we have generated a pipeline of potentially disease-modifying therapies that address the known root causes of rare genetic diseases. The following chart summarizes key information about our pipeline of clinical stage and pre-clinical programs.



Our Strategy

Through our focus on the development of small molecules, including our product candidate for the treatment of SCD, our aim is to address unmet need in patients with genetically defined rare diseases that are debilitating and, in the case of SCD, life-threatening. The key components of our strategy include:

- ***Rapidly develop pociredir for the treatment of SCD.*** We aim to rapidly complete the clinical development of pociredir for the treatment of SCD to support regulatory approval. We expect to provide clinical data from the 12 mg dose cohort in mid-2025 and from the 20 mg dose cohort by the end of 2025, with each cohort expected to enroll approximately 10 patients.

- ***Continue to apply our discovery efforts including pursuing in-licensing or acquisition opportunities to grow our portfolio of product candidates for the treatment of genetically defined rare diseases.*** We have developed a discovery approach that we employ to systematically identify and validate cellular drug targets that can potentially modulate gene expression to treat known root causes of genetically defined rare diseases, with a primary focus on hematology diseases. We also seek to explore opportunities to acquire or in-license complementary technologies or therapies, such as our exclusive global license agreement with CAMP4 Therapeutics Corp., or CAMP4.

- ***Maximize the commercial potential of our product candidates.*** We have retained all rights to our lead product candidate, and we plan to commercialize any approved product for such rare genetically defined diseases using a targeted sales infrastructure. We may in the future pursue commercialization partnerships for certain product candidates and/or markets outside the United States.

Pociredir

We are developing pociredir, which is designed to elevate the level of fetal hemoglobin, or HbF, for the treatment of people with SCD. We also believe that people with some types of ß-thalassemia may benefit from treatment with pociredir.

Overview of Sickle Cell Disease

Sickle cell disease is a genetic disorder of RBCs. The root cause of SCD is a mutant hemoglobin that polymerizes in low oxygen conditions. This polymerization creates the abnormal, elongated, or sickle, shape of the RBC and results in, ultimately, hemolysis and vascular injury that causes major morbidities and significantly limits lifespan in people with SCD. People with SCD typically suffer from serious clinical consequences, which may include vaso-occlusive crises, anemia, pain, infections, stroke, heart disease, pulmonary hypertension, kidney failure, liver disease and reduced life expectancy. According to a study published by the American Medical Association, approximately 32.5% of adults with SCD were hospitalized three or more times per year due to pain crises. SCD is reported to shorten life expectancy by approximately 20 to 30 years. People with SCD are primarily treated by hematologists.

In the United States, where newborn screening for SCD is mandatory, the estimated prevalence is approximately 100,000 individuals. In Europe, the estimated prevalence is approximately 50,000 individuals. According to the World Health Organization, the global incidence is estimated to be approximately 300,000 births annually. SCD is most prevalent in Africa and the Middle East.

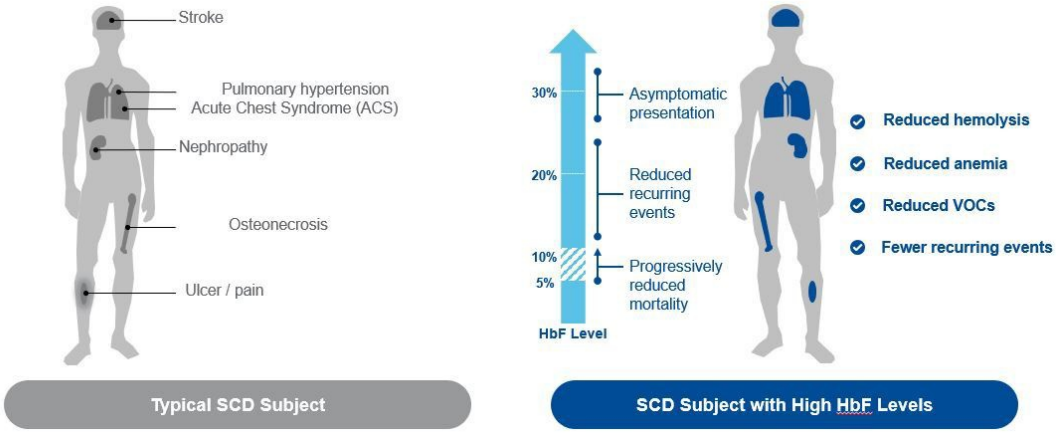
Several approved drug treatments for SCD focus primarily on the management and reduction of painful vaso-occlusive crises, and improvement of hemolytic anemia, as well as gene therapies for the treatment of severe SCD. Despite ongoing efforts to develop and commercialize treatments for SCD, we believe there is still a high unmet need that could be better addressed by a small molecule, oral therapy capable of increasing HbF production. See "Competition" for a more comprehensive description of the competitive landscape in SCD.

SCD Biology

SCD is caused by a mutation in the *HBB* gene. This gene encodes a protein that is a key component of hemoglobin, a protein complex whose function is to transport oxygen in the body. Hemoglobin in adults is a complex of four proteins, two hemoglobin ß-subunits and two hemoglobin α-subunits. In people with SCD, hemoglobin is composed of two mutant ß-subunits and two α-subunits and the result is the formation of sickle hemoglobin, or HbS. The result of the mutation is less efficient oxygen transport and the formation of RBCs that have a sickle shape. These sickle shaped cells are much less flexible than healthy cells and can block blood vessels (vaso-occlusion) or rupture (lysis), leading to pain, anemia, irreversible organ damage or even death.

During fetal development, the major form of hemoglobin is HbF. Similar to hemoglobin in adults, HbF is also a complex of four proteins, two α-subunits and two γ-subunits. Shortly after birth, the genes encoding the γ-subunits, the *HBG1* and *HBG2* genes, are silenced and the *HBB* gene is activated. As described above, SCD is caused by a mutation in the *HBB* gene that gives rise to mutated ß-subunits.

A small subset of individuals with the sickle cell mutation continue to produce high levels of HbF due to inheritance of additional genetic mutations, which is called Hereditary Persistence of HbF, or HPFH. Individuals with elevated HbF exhibit minimal clinical manifestations of SCD. A recent analysis demonstrated that each 1% increase in HbF levels is associated with a 4%-8% annualized reduction in vaso-occlusive crises, or VOCs. Additionally, HbF levels in the mid-to-high twenties have been shown to result in a near abolition of VOCs.



Our Approach to Address the Root Cause of SCD

Our strategy to address the root cause of SCD was to identify a drug mechanism that induces expression of HbF. We believe that pociredir may address the root cause of SCD through this mechanism of action.

Identification of the Drug Target for SCD

We conducted target identification and validation activities using human umbilical cord blood-derived erythroid progenitor 2, or HUDEP2, cells as a model to study HbF reactivation. HUDEP2 cells are immature RBCs. By screening our small molecule probe library and a CRISPR library, we identified several potential drug targets that activated the *HBG1/2* genes and resulted in HbF elevation. Each screening approach identified the same protein complex, PRC2, which we believe plays an important role in the expression of genes responsible for the production of HbF. We conducted additional validation experiments in which we observed that inhibition of several components of this complex resulted in the desired elevation of HbF. We also observed that inhibition of these components did not adversely affect important cell health markers.

We selected a component of this protein complex, EED, for drug discovery activities following an assessment of its tractability as a drug target. The normal physiological role of EED is to facilitate a post-translational protein modification, and the goal of our medicinal chemistry program was to optimize inhibitors of EED. We developed *in vitro* and *in vivo* target engagement assays, as well as enabled X-ray crystallography, to discover and develop pociredir, a novel small molecule inhibitor of the EED subunit of PRC2.

Pociredir

Pociredir is an oral HbF inducer that is in development for SCD. Pociredir is designed to bind to EED and inhibit the transcriptional silencing activity of PRC2. Inhibition of EED leads to potent downregulation of key fetal globin repressors, including BCL11A, thereby causing an increase in HbF. EED is a member of the PRC2 complex, which also includes EZH2. There are approved products in the EZH2 class of medications and their approved labeling outlines safety risks, including an increased risk of hematologic malignancies. We initiated our Phase 1b clinical trial of pociredir in SCD in the fourth quarter of 2021. In February 2022, the FDA granted orphan drug designation to pociredir for the treatment of SCD. In December 2022, the FDA granted fast track designation to pociredir for SCD. In February 2023, the FDA placed the IND for pociredir for the potential treatment of SCD on full clinical hold. Accordingly, we suspended enrollment and dosing in the Phase 1b trial of pociredir and withdrew our separate IND for pociredir in *β*-thalassemia. The FDA's clinical hold referenced the data from toxicology studies in rats and dogs that we submitted to the IND in April, October, and December 2022, as well as a response to an early February 2023 information request from the FDA about these toxicology studies that we submitted in mid-February 2023.

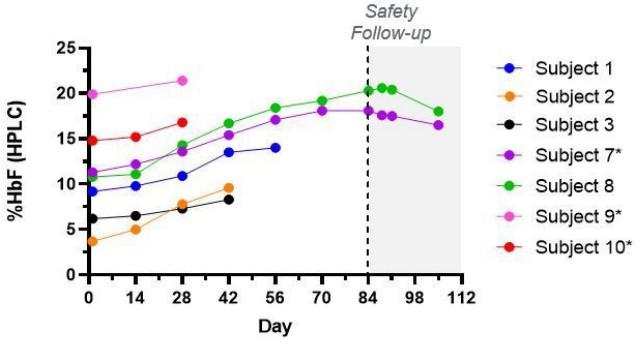
As part of our pociredir development program, we have conducted numerous non-clinical toxicology studies, including studies conducted under good laboratory practice, or GLP. These toxicology studies have included repeat-dose maximum tolerated dose and dose range finding studies; 28-day, 13-week, 17-week, and 26-week studies in rats; and 28-day, 13-week, and 39-week studies in dogs. In connection with the clinical hold, the FDA noted that the profile of hematological malignancies observed in the toxicology studies of pociredir is similar to that observed with other inhibitors of PRC2 and that hematological malignancies have been reported clinically with other inhibitors of PRC2.

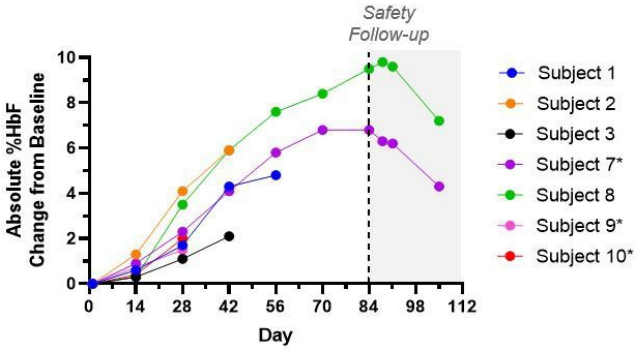
In August 2023, the FDA lifted the full clinical hold on the IND for pociredir for the potential treatment of SCD. The Phase 1b clinical trial has been re-initiated at the 12 mg once daily dose level, with that cohort expected to enroll approximately 10 patients, followed by an additional cohort of approximately 10 patients at the 20 mg once daily dose level. Patients are evaluated over a 12-week treatment period. The protocol was amended to revise the inclusion and exclusion criteria to target patients with higher disease severity. Key inclusion criteria includes patients with certain frequencies of vaso-occlusive crises and/or other specified measures of severity, previous experience with hydroxyurea, and previous experience with a stable dose of voxelotor, crizanlizumab, or L-glutamine or lack of access to these advanced therapies. Key exclusion criteria excludes subjects currently on or having received hydroxyurea within 60 days prior to initiating pociredir.

Clinical Trial: Phase 1b

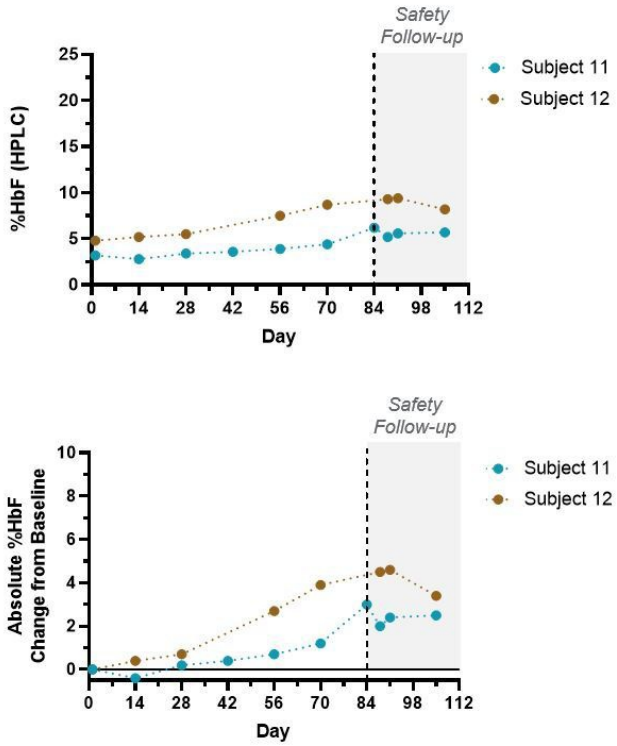
In January 2023, we announced Phase 1b data from subjects in the 6 mg dose cohort, as well as completion of enrollment in the 6 mg and 2 mg dose cohorts and commencement of enrollment in the 12 mg dose cohort. Until being placed on clinical hold in February 2023, the Phase 1b trial was evaluating subjects both on and off background hydroxyurea therapy.

Phase 1b data from subjects in the 6 mg dose cohort (n=10) showed up to 9.5% absolute HbF increases from baseline. These data suggested no difference in response in subjects on (n=3) and off (n=7) background hydroxyurea. We also observed improved biomarkers of hemolysis in evaluable subjects dosed at 6 mg. The figures below illustrate percentage HbF increase by high-performance liquid chromatography, or HPLC and absolute percentage HbF change from baseline for evaluable subjects (n=7) in the 6 mg dose cohort. Subjects with asterisks were on background hydroxyurea.

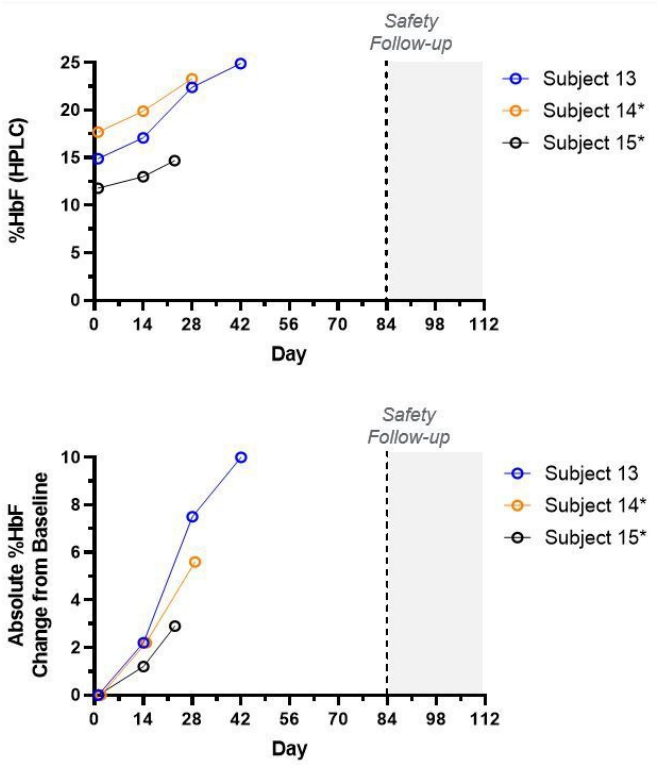




We have completed enrollment and dosing in the 6 mg and 2 mg dose cohorts. Data from subjects in the 2 mg dose cohort (n=2), showed up to 4.6% absolute HbF increases from baseline.



Data from subjects in the 12 mg dose cohort (n=3), prior to the suspension of the trial in February 2023, showed up to 10.0% absolute HbF increases from baseline, or total HbF of ~25.0%, after 42 days of treatment (the full three months of treatment was interrupted by the clinical hold). Subjects with asterisks were on background hydroxyurea.



Increases in HbF have been shown to reduce the frequency or severity of a broad range of SCD symptoms, including VOC, anemia, pain, infection, stroke and others. Based on a large body of genetic, clinical, and observational evidence showing the effects of higher levels of HbF in people with SCD, for a given patient, even small increases in total HbF are associated with clinical benefit, with levels in the upper 20% to lower 30%-range being associated with significant reductions in the manifestations of SCD. We believe the initial data showing that pociredir increases HbF levels by up to ~10.0% from baseline after as few as six weeks of therapy support its potential to become a transformative therapy for people living with SCD.

Pociredir was generally well-tolerated through the end of 2023. There have been 23 treatment emergent adverse events, or TEAEs, reported as of the data cutoff date, eight of which were reported as possibly related to study drug (headache, lip numbness, diarrhea, fatigue, somnolence, nausea or tinnitus), none of which were severe and were deemed non-serious. There have been no discontinuations due to TEAEs as of the data cutoff date. Four of the 23 TEAEs were characterized as VOCs, and were deemed unrelated to pociredir; one of these was reported as a serious adverse event, or SAE, with acute chest syndrome in a subject who was non-adherent to study drug administration.

Clinical Trial: Phase 1 Healthy Volunteers

In the fourth quarter of 2020, we initiated a Phase 1 clinical trial of pociredir in healthy adult volunteers. The Phase 1 randomized, double-blind, placebo-controlled trial was designed to evaluate the safety, tolerability, and pharmacokinetics, or PK, of ascending doses of pociredir. In the single ascending dose, or SAD, cohorts, healthy volunteers received one dose of either placebo or 2, 4, 10, 20, 30, 40 or 60 mg of pociredir. In the multiple ascending dose, or MAD, cohorts, healthy volunteers received a once-daily dose of placebo or 2, 6, 10, 20 or 30 mg of pociredir for 14 consecutive days. Each MAD cohort had six subjects on drug and two on placebo. Food effect was also studied in a separate 20 mg dose cohort. Exploratory measures were included in the MAD cohorts to assess target engagement, changes in human hemoglobin messenger RNA, or HBG mRNA, and HbF-containing reticulocytes, or F-reticulocytes.

We reported data from the 2, 4, 10, 20, 30 and 40 mg SAD cohorts and the 2, 6 and 10 mg MAD cohorts in healthy volunteers in August 2021, and we reported data from the 60 mg SAD cohort and the 20 and 30 mg MAD cohorts in healthy volunteers, as well as data from the 20 mg cohort assessing food effect in December 2021.

Pociredir was generally well-tolerated in healthy adult volunteers with no SAEs reported and no discontinuations due to TEAEs across all SAD and MAD cohorts. Data continued to show dose-proportional PK, with a mean half-life of approximately 6-7 hours in the MAD cohorts, supporting once-daily dosing, and no food effect was observed with pociredir. Data from the MAD cohorts continued to show robust target engagement, as evidenced by an approximately 75-95% reduction from baseline in H3K27me3 after 14 days of treatment. Based on our preclinical studies, this level of target engagement is predicted to result in robust induction of *HBG1/2* and subsequently increase HbF production.

Data from the MAD cohorts also showed time- and dose-dependent HBG mRNA induction, as shown in the chart below, demonstrating proof-of-biology. Persistent HBG mRNA induction was observed for 7-10 days after treatment. In preclinical studies of pociredir, increases in HBG mRNA have consistently translated to the same fold increases in HbF protein.

HBG mRNA Mean Fold Induction for pociredir versus Placebo

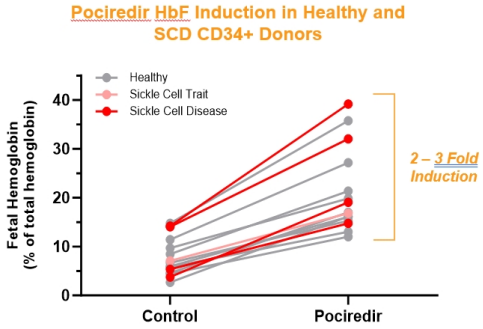
	2 mg*		6 mg*		10 mg*		20 mg		30 mg	
	Mean Fold Induction	P-value	Mean Fold Induction	P-value	Mean Fold Induction	P-value	Mean Fold Induction	P-value	Mean Fold Induction	P-value
Day 7	1.28	0.3494	1.94	0.0135	2.08	0.0063	2.06	0.0072	2.29	0.0025
Day 14	1.20	0.5122	2.45	0.0025	3.54	<0.0001	5.63	<0.0001	6.15	<0.0001
Safety Follow-up (Day 21-24)	1.21	0.3736	2.75	<0.0001	3.22	<0.0001	6.45	<0.0001	6.13	<0.0001

Pociredir Activity in Preclinical Studies

We have observed *in vitro* and *in vivo* activation of the *HBG1/2* genes in preclinical studies with pociredir. We observed that pociredir elevated levels of HbF with minimal adverse effects on important cellular health markers. As depicted in the graphic below, we also observed *in vitro* upregulation of HbF in primary human CD34+ cells differentiated into RBCs from 14 donors, including nine different healthy human donors, four SCD donors and one sickle cell trait donor, after seven days of drug treatment. Pociredir showed a significant elevation of HbF over baseline in each of these 14 donor cell lines. We have conducted additional preclinical profiling in CD34+ derived cells and observed that treatment with pociredir increased HbF levels to approximately 30% of total hemoglobin, as measured by mass spectrometry, high performance liquid

chromatography, and fast protein liquid chromatography techniques. Notably, based on a review of data from other mechanisms, HbF fold induction in CD34+ cells has translated reliably into the clinic.

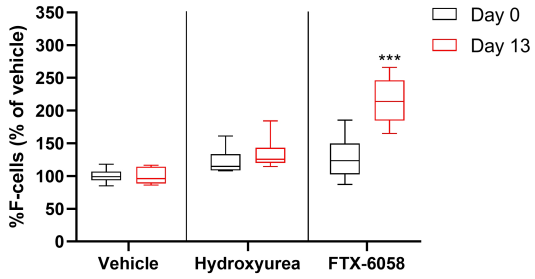
Effect of pociredir treatment in differentiated primary human CD34+ cells



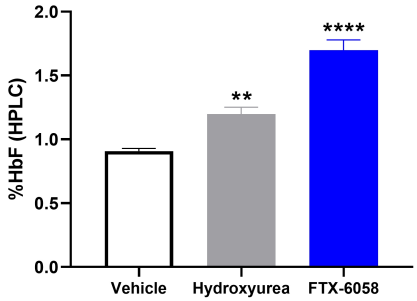
Additionally, we compared the effect of pociredir in CD34+ derived cells relative to that of hydroxyurea. We observed that hydroxyurea had a minimal impact on HbF elevation, whereas we observed that pociredir significantly elevated HbF. In cells treated with the combination of pociredir and hydroxyurea, we observed an increased effect relative to either compound alone.

Additionally, we studied pociredir in a mouse model of SCD, known as the Townes mouse model. In this model, mouse globin genes have been replaced with human globin genes, thereby allowing investigations of mechanisms that may regulate human hemoglobin gene expression. The Townes mouse model has been widely used to study potential treatments for SCD. As shown in the figures below, we observed that pociredir resulted in a significant increase in HbF-expressing cells, or F-cells, and HbF protein levels after 13 days of dosing at 5 mg/kg once per day whereas hydroxyurea resulted in modest increases in F-cells and HbF.

Percentage of F-cells in Townes mice treated with pociredir



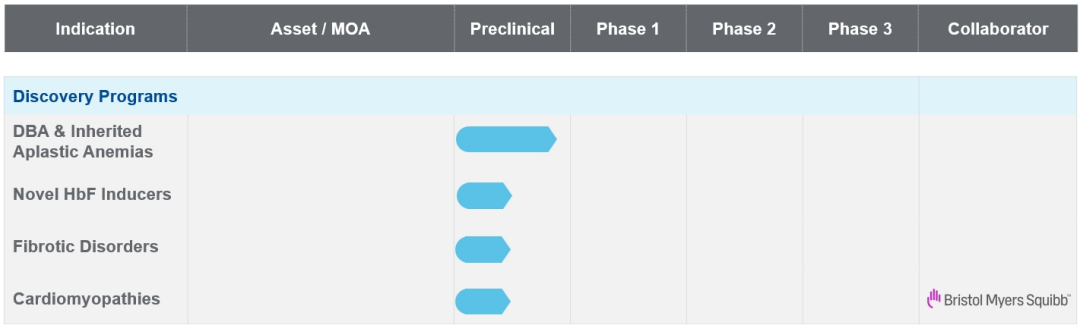
HbF protein levels in Townes mice treated with pociredir



In the graphic on the left, we quantified the percentage of F-cells as a percentage of total cells (%F-cells) for the three treatment conditions from mouse blood, shown as a percentage of vehicle-alone-treated SCD mice. In the graphic on the right, we determined the level of human HbF protein for the three treatment conditions, quantifying HbF protein as a percentage of total hemoglobin. Each value represents the mean value from eight mice per treatment after 13 days of treatment. In these studies, we used a conventional method of assessing statistical significance known as a one-way analysis of variance, or ANOVA. The p-value for pociredir was less than 0.001 for both studies and the p-value for hydroxyurea in the study depicted on the right was less than 0.01.

Discovery Programs

We have utilized our expertise to discover the target that we are pursuing with a small molecule for SCD. We are leveraging our discovery approach to discover drug targets for other rare, genetically defined diseases. We continue to advance our program for the potential treatment of inherited aplastic anemias, such as Diamond-Blackfan anemia (DBA), Shwachman-Diamond syndrome, and Fanconi anemia, and we plan to submit an IND for DBA during the fourth quarter of 2025.



License Agreements and Collaborations

Collaboration and License Agreement with MyoKardia, a wholly-owned subsidiary of Bristol-Myers Squibb Company

In July 2020, we entered into a collaboration and license agreement with MyoKardia to identify biological targets that are capable of modulating genes of interest with relevance to certain genetically defined cardiomyopathies. Under the terms of the agreement, we granted MyoKardia an exclusive worldwide license under certain intellectual property rights to research, develop, make, have made, use, have used, sell, have sold, offer for sale, have offered for sale, import, have imported, export, have exported, distribute, have distributed, market, have marketed, promote, have promoted, or otherwise exploit products directed against certain biological targets identified by us that are capable of modulating certain genes of interest with relevance to certain genetically defined cardiomyopathies.

Pursuant to a mutually agreed research plan, we will perform assay screening and related research activities to identify and validate up to a specified number of potential cardiomyopathy gene targets, or the Identified Targets, for further research, development, manufacture and commercialization by MyoKardia. We and MyoKardia will work together to determine how best to advance at each stage of the research activities under the research plan and to identify which of the Identified Targets, if any, meet the criteria set forth in the research plan, or the Cardiomyopathy Target Candidates. Upon completion of the research plan, the parties will work together to prepare a final data package and MyoKardia may designate certain Cardiomyopathy Target Candidates for MyoKardia's further exploitation under the agreement, or the Cardiomyopathy Targets. If MyoKardia does not designate any Cardiomyopathy Targets during the designated period, then the agreement will automatically terminate. If MyoKardia designates one or more Cardiomyopathy Targets, then MyoKardia will be obligated to use commercially reasonable efforts to seek regulatory approval for and to commercialize one product directed against an Identified Target in certain specified countries.

During the period in which we are performing the research activities pursuant to the research plan, or the Research Term and for a specified period beyond the Research Term if MyoKardia designates a Cardiomyopathy Target, we may only use the data generated from such research activities for MyoKardia in accordance with the agreement. During the Research Term and for a specified period thereafter, we may not research, develop, manufacture, commercialize, use, or otherwise exploit any compound or product (a) that is a compound or product under the agreement that is directed against the Cardiomyopathy Target Candidates for the treatment, prophylaxis, or diagnosis of any indication or (b) for the treatment of any genetically defined cardiomyopathies shown to be related to certain specified genes of interest that are modulated by the Cardiomyopathy Targets.

Under the agreement, MyoKardia made a $10.0 million upfront payment and a $2.5 million payment as prepaid research funding to us in July 2020. MyoKardia will also reimburse us for the costs of the research activities not covered by the prepaid research funding, up to a maximum amount of total research funding (including the prepaid research funding). Upon the achievement of specified preclinical, development and sales-based milestones, we will be entitled to preclinical milestone payments, development milestone payments and sales-based milestone payments of up to $298.5 million in the aggregate per target for certain Identified Targets, and of up to $150.0 million in the aggregate per target for certain other Identified Targets. To date, we have achieved a $2.5 million specified preclinical milestone. MyoKardia will also pay us tiered royalties ranging from a mid single-digit percentage to a low double-digit percentage based on MyoKardia's, and any

of its affiliates' and sublicensees', annual worldwide net sales of products under the agreement directed against any Identified Target. The royalties are payable on a product-by-product basis during a specified royalty term, and may be reduced in specified circumstances.

The agreement continues on a country-by-country and product-by-product basis until the expiration of the last to expire royalty term for a product, at which time the agreement expires with respect to such product in such country, unless the agreement is terminated earlier in accordance with its terms. Either party has the right to terminate the agreement if the other party has materially breached in the performance of its obligations and such breach has not been cured within the applicable cure period. MyoKardia also has the right to terminate the agreement for convenience in its entirety or on a target-by-target, product-by-product or molecule-by-molecule basis, upon prior written notice to us.

License Agreement with CAMP4

In July 2023, we entered into a license agreement with CAMP4 pursuant to which we received a worldwide exclusive license (including the right to sublicense) from CAMP4 to rights under its DBA program, which includes certain small molecule compounds, composition of matter and method of use patent rights, and know-how for us to research, develop, manufacture, use, commercialize or otherwise exploit therapeutic products in any indication, including the grant of a sublicense under certain intellectual property rights that CAMP4 has licensed under an agreement with Children's Medical Center Corporation, or CMCC.

We made an undisclosed upfront non-refundable, non-creditable payment to CAMP4. If we succeed in developing and commercializing licensed products, CAMP4 will be eligible to receive (i) up to $35.0 million in development and regulatory milestone payments, and (ii) up to $35.0 million in sales milestone payments. CAMP4 is also eligible to receive royalties on worldwide net sales of licensed products ranging from mid-single digit to low-double digit, subject to potential reduction following loss of patent coverage, the launch of certain generic products or royalty stacking for licenses of third party intellectual property. The royalties will expire on a product-by-product and country-by-country basis upon the latest to occur of (i) the expiration of all valid patent claims covering the compounds in such country, (ii) the expiration of all regulatory exclusivities in such country, and (iii) 10 years following the first commercial sale of in such country. We are responsible for the costs associated with the development and regulatory approvals of licensed products.

Unless earlier terminated in accordance with its terms, the license agreement continues on a country-by-country and licensed product-by-licensed product basis until the expiration of the royalty term in each country, at which time the license agreement expires with respect to such licensed product in such country and we will have a fully-paid up, royalty-free and perpetual license to the licensed patent rights and know-how with respect to such licensed product in such country. CAMP4 has the right to terminate the license agreement in the event of our non-payment (subject to cure periods and tolling for bona fide disputes). CAMP4 may also terminate the license agreement if we challenge certain patents sublicensed to us by CAMP4. Either party may terminate the license agreement in its entirety for the other party's material breach if such other party fails to cure the breach. Either party may also terminate the agreement in its entirety upon certain insolvency events involving the other party. We have the right to terminate the license agreement with CAMP4 for any or no reason upon prior written notice to CAMP4.

Losmapimod Agreements

In May 2024, we entered into a collaboration and license agreement Sanofi pursuant to which we granted Sanofi an exclusive license under certain intellectual property rights to commercialize losmapimod for the treatment of FSHD outside of the United States. On December 18, 2024, we received written notice of Sanofi's election to terminate for convenience the collaboration and license agreement. In accordance with the agreement, the termination will become effective on April 17, 2025, which is 120 days following the date of receipt of the notice by us.

In February 2019, we entered into a right of reference and license agreement with affiliates of GSK, as amended in September 2020, pursuant to which GSK granted us a right of reference to certain INDs filed with the FDA and controlled by GSK or its affiliates relating to losmapimod and an exclusive worldwide license under certain patent rights related to losmapimod. The agreement also provides us with an exclusive worldwide license to certain of GSK's preclinical and clinical data with respect to losmapimod.

See Note 10 to our consolidated financial statements included elsewhere in this Annual Report on Form 10-K for a description of license agreements with Sanofi and GSK.

Intellectual Property

We strive to protect and enhance our discovery approach, inventions and improvements that are commercially important to the development of our business, including by seeking, maintaining and defending patent rights, whether developed internally or licensed from third parties. We also rely on trade secrets, know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen and maintain our proprietary position in our field.

Our future commercial success depends, in part, on our ability to: obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business; defend and enforce in our intellectual property rights, in particular our patents rights; preserve the confidentiality of our trade secrets; and operate without infringing, misappropriating or violating the valid and enforceable patents and proprietary rights of third parties. Our ability to stop third parties from making, using, selling, offering to sell or importing our products may depend on the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities.

The patent positions of biotechnology and pharmaceutical companies like ours are generally uncertain and can involve complex legal, scientific and factual issues. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient proprietary protection from competitors. We also cannot ensure that patents will issue with respect to any patent applications that we or our licensors may file in the future, nor can we ensure that any of our owned or licensed patents or future patents will be commercially useful in protecting our product candidates and methods of manufacturing the same. In addition, the coverage claimed in a patent application may be significantly reduced before a patent is issued, and its scope can be reinterpreted and even challenged after issuance. As a result, we cannot guarantee that any of our products will be protected or remain protectable by enforceable patents. Moreover, any patents that we hold may be challenged, circumvented or invalidated by third parties. See "Risk Factors—Risks Related to Our Intellectual Property" for a more comprehensive description of risks related to our intellectual property.

We generally file patent applications directed to our key programs in an effort to secure our intellectual property positions vis-a-vis these programs. As of February 18, 2025, we owned or in-licensed eight U.S. patents, nine U.S. pending non-provisional patent applications and related pending foreign patent applications, and one pending U.S. provisional patent application.

The intellectual property portfolio for our most advanced programs as of February 18, 2025, is summarized below. Prosecution is a lengthy process, during which the scope of the claims initially submitted for examination by the U.S. Patent and Trademark Office may be significantly narrowed before issuance, if issued at all. We expect this may be the case with respect to some of our pending patent applications referred to below.

Pociredir

Currently, our patent portfolio related to pociredir includes three issued U.S. patents directed to composition of matter that is expected to expire in 2040, one U.S. non-provisional application and related granted patents and pending patent applications in Canada and Mexico, Europe, Africa, Australia and New Zealand, South America, and Asia that, if issued, are expected to expire between 2039 and 2040. We also own three U.S. non-provisional applications and related patent applications pending in Europe directed to solid forms and methods of using pociredir and one pending U.S. non-provisional application directed to pociredir methods of use and formulations, that, if resulting in issued patents, would be expected to expire between 2042 and 2043.

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

In the United States, the term of a patent covering an FDA-approved drug may, in certain cases, be eligible for a patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984 as compensation for the loss of patent term during the FDA regulatory review process. The period of extension may be up to five years, but cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval. Only one patent among those eligible for an extension and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended. Similar provisions are available in Europe and in certain other jurisdictions to extend the term of a patent that covers an approved drug. It is possible that issued U.S. patents covering the use of losmapimod and products from our intellectual property may be entitled to patent term extensions. If our use of drug candidates or the drug candidate itself receive FDA approval, we intend to apply for patent term extensions, if available, to extend the term of patents that cover the approved use or drug candidate. We also intend to seek patent term extensions in any jurisdictions where available, however, there is no guarantee that the applicable authorities, including the FDA, will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such extensions.

In addition to patent protection, we rely upon unpatented trade secrets and confidential know-how and continuing technological innovation to develop and maintain our competitive position. However, trade secrets and confidential know-how are difficult to protect. We seek to protect our proprietary information, in part, using confidentiality agreements with any collaborators, scientific advisors, employees and consultants and invention assignment agreements with our employees. We also have agreements requiring assignment of inventions with selected consultants, scientific advisors and collaborators. These agreements may not provide meaningful protection. These agreements may also be breached, and we may not have an adequate remedy for any such breach. In addition, our trade secrets and/or confidential know-how may become known or be independently developed by a third party, or misused by any collaborator to whom we disclose such information. Despite any measures taken to protect our intellectual property, unauthorized parties may attempt to copy aspects of our products or to obtain or use information that we regard as proprietary. Although we take steps to protect our proprietary information, third parties may independently develop the same or similar proprietary information or may otherwise gain access to our proprietary information. As a result, we may be unable to meaningfully protect our trade secrets and proprietary information. See "Risk Factors—Risks Related to our Intellectual Property" for a more comprehensive description of risks related to our intellectual property.

Manufacturing

We do not have any manufacturing facilities. We have obtained sufficient quantities of pociredir from a contract manufacturing organization to complete our Phase 1b clinical trial.

We expect to continue to rely on third parties for the manufacture of pociredir for any future clinical trials and for the manufacture of any future product candidates for preclinical and clinical testing, as well as for commercial manufacture if our product candidates receive marketing approval. Our lead product candidate is a small molecule and can be manufactured in reliable and reproducible synthetic processes from readily available starting materials. We expect to continue to develop product candidates that can be produced cost-effectively at contract manufacturing facilities.

Competition

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

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industry may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

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

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval or emergency use authorizations for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic products. If our product candidates achieve marketing approval, we expect that they will be priced at a significant premium over competitive generic products.

If our lead product candidates are approved for the indications for which we are currently undertaking clinical trials, they will compete with the therapies and currently marketed drugs discussed below.

SCD

Several approved drug treatments for SCD focus primarily on the management and reduction of painful vaso-occlusive crises, and improvement of hemolytic anemia. The five drug treatments approved in the United States are hydroxyurea, crizanlizumab, L-glutamine, lovo-cel, and exa-cel. Hydroxyurea is approved for the treatment of SCD to reduce the frequency of painful crises and to reduce the need for blood transfusions. Hydroxyurea is available in both generic and brand name formulations including DROXIA manufactured by Bristol-Myers Squibb, and SIKLOS manufactured by Addmedica. Crizanlizumab, a fully-human monoclonal antibody p-selectin inhibitor marketed by Novartis as ADAKVEO, is approved for the reduction in the frequency of VOCs. L-glutamine, brand name ENDARI, marketed by Emmaus Life Sciences, Inc., is approved to reduce acute complications of the disorder.

Lovo-cel and exa-cel are gene therapies approved for the treatment of severe SCD. Lovo-cel, brand name LYFGENIA, is a gene therapy designed to add functional copies of a modified form of the β-globin gene into patient's hematopoietic stem cells (HSCs), to make normally functioning RBCs. Exa-cel, brand name CASGEVY, is a gene therapy consisting of autologous CD34+ cells edited by CRISPR/Cas9-technology to decrease BCL11A expression, resulting in increased HbF production. Gene therapies need to be administered in an in-patient procedure known as HSCT. As part of the transplant process, the patient receives myeloablative chemotherapy to remove the original unedited stem cells in the bone marrow in order to enable the genetically modified stem cells to engraft.

Additionally, voxelotor, brand name OXBRYTA, a hemoglobin polymerization inhibitor that was approved under accelerated approval, was voluntarily withdrawn by Pfizer Inc. from worldwide markets in September 2024.

An additional potentially curative treatment currently approved for severe SCD populations is allo-HSCT. However, allo-HSCT is more commonly offered to pediatric individuals with an available HLA-matched sibling donor. The 5-year survival rates in this young population is quite high but for older individuals (>16 years), the survival rates can be considerably lower. There are also significant risks associated with allo-HSCT including infertility and graft-versus-host disease.

A supportive care option for management of SCD is red blood cell transfusion but this can potentially be complicated by alloimmunization, transfusion reactions, and iron overload.

Pociredir could face competition from a number of different therapeutic approaches in development for people with SCD. Novo Nordisk A/S, or Novo, is evaluating NDec (decitabine-tetrahydrouridine), a combination of two small molecules designed to increase production of HbF, in a Phase 2 clinical trial. Novartis is evaluating ITU-512, a small molecule designed to increase production of HbF, in a Phase 1/2 clinical trial comprised of a Phase 1 trial in healthy volunteers and a Phase 2 trial in subjects with SCD. Bristol-Myers Squibb is evaluating BMS-986470, a small molecule designed to increase production of HbF, in a Phase 1/2a clinical trial in healthy volunteers and subjects with SCD. GSK is evaluating GSK4172239D, a small molecule designed to increase production of HbF, in a Phase 1 clinical trial in subjects with SCD. Novo is also evaluating etavopivat, a pyruvate kinase activator, or PK activator, in a Phase 2/3 clinical trial. Agios Pharmaceuticals, Inc., or Agios, is evaluating mitapivat, a PK activator, in a Phase 2/3 clinical trial in subjects with SCD. Agios also anticipates initiating a Phase 2 clinical trial in mid-2025 to evaluate tebapivat, a PK activator, in subjects with SCD. Pfizer, Inc. is evaluating osivelotor, an HbS polymerization inhibitor, in a Phase 2/3 clinical trial and inclacumab, a P-selectin inhibitor that is being evaluated in a Phase 3 clinical trial. Beam Therapeutics is evaluating BEAM-101, an autologous base edited CD34+ HSPC designed to increase production of HbF, in a Phase 1/2 clinical trial in subjects with severe SCD.

Government Regulation and Product Approvals

Government authorities in the United States at the federal, state and local level, and in other countries and jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, manufacture, pricing, reimbursement, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of biopharmaceutical products. The processes for obtaining marketing approvals in the United States and in foreign countries and jurisdictions, along with compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

Approval and Regulation of Drugs in the United States

In the United States, drug products are regulated under the Federal Food, Drug and Cosmetic Act, or FDCA, and applicable implementing regulations and guidance. The failure of an applicant to comply with the applicable regulatory requirements at any time during the product development process, including non-clinical testing, clinical testing, the approval

process or post-approval process, may result in delays to the conduct of a study, regulatory review and approval and/or administrative or judicial sanctions.

An applicant seeking approval to market and distribute a new drug in the United States generally must satisfactorily complete each of the following steps before the product candidate will be approved by the FDA:

- preclinical testing including laboratory tests, animal studies and formulation studies, which must be performed in accordance with the FDA's GLP regulations and standards;
- submission to the FDA of an IND for human clinical testing, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials to establish the safety and effectiveness of the product candidate for each proposed indication, in accordance with current good clinical practices, or GCP;
- preparation and submission to the FDA of a new drug application, or NDA, for a drug product which includes not only the results of the clinical trials, but also, detailed information on the chemistry, manufacture and quality controls for the product candidate and proposed labelling for one or more proposed indication(s);
- review of the product candidate by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities, including those of third parties, at which the product candidate or components thereof are manufactured to assess compliance with current good manufacturing practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- satisfactory completion of any FDA audits of the non-clinical and clinical trial sites to assure compliance with GCP and the integrity of clinical data in support of the NDA;
- payment of user fees and securing FDA approval of the NDA to allow marketing of the new drug product; and
- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and the potential requirement to conduct any post-approval studies required by the FDA.

Preclinical Studies

Before an applicant begins testing a product candidate with potential therapeutic value in humans, the product candidate enters the preclinical testing stage, including *in vitro* and animal studies to assess the safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. Preclinical tests include laboratory evaluations of product chemistry, formulation and stability, as well as other studies to evaluate, among other things, the toxicity of the product candidate. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements, including GLP regulations and standards. The results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity and long-term toxicity studies may continue after the IND is submitted.

The IND and IRB Processes

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their voluntary informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND.

An IND is an exemption from the FDCA that allows an unapproved product candidate to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer such investigational product to humans. Such authorization must be secured prior to interstate shipment and administration of any product candidate that is not the subject of an approved NDA. In support of a request for an IND, applicants must submit a protocol for each clinical trial, and any subsequent protocol amendments must be submitted to the FDA as part of the IND. The FDA

requires a 30-day waiting period after the filing of each IND before clinical trials may begin. This waiting period is designed to allow the FDA to review the IND to determine, among other things, whether human research subjects will be exposed to unreasonable health risks. At any time during this 30-day period, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold or partial clinical hold. In these cases, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. Clinical holds are imposed by the FDA whenever there is concern for patient safety and may be a result of new data, findings, or developments in clinical, nonclinical, and/or chemistry, manufacturing, and controls areas. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a specific protocol or part of a protocol may not be allowed to proceed, while other protocols may be allowed. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following issuance of a clinical hold or partial clinical hold, a clinical trial may only resume after the FDA has notified the sponsor. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the clinical trial can proceed.

A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived. When a foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with certain regulatory requirements, including GCP requirements, of the FDA in order to use the study as support for an IND or application for marketing approval. The GCP requirements encompass both ethical and data integrity standards for clinical studies. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign studies are conducted in a manner comparable to that required for IND studies.

In addition to the foregoing IND requirements, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove the study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. An IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements, the protocol, or other requirements or if the product candidate has been associated with unexpected serious harm to patients.

Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee. This group provides authorization as to whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the study.

Suspension or termination of development during any phase of clinical trials can occur for many reasons, including if the FDA, an IRB, a data safety monitoring board, or we determine that the participants or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made by us based on factors such as evolving business objectives and/or the competitive environment.

Information about certain clinical trials must be submitted within specific timeframes to the NIH for public dissemination on its ClinicalTrials.gov website. Similar requirements for posting clinical trial information are present in the European Union and other countries, as well.

Expanded Access to an Investigational Drug for Treatment Use

Expanded access, sometimes called "compassionate use," is the use of investigational new drug products outside of registrational clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options. The rules and regulations related to expanded access are intended to improve access to investigational drugs for patients who may benefit from investigational therapies that do not conflict with registrational trials. FDA regulations allow access to investigational drugs under an IND by the company or the treating physician for treatment purposes on a case-by-case basis for: individual patients (single-patient IND applications for treatment in emergency settings and non-emergency settings); intermediate-size patient populations; and larger populations for use of the drug under a treatment protocol or Treatment IND Application.

When considering an IND application for expanded access to an investigational product, the FDA will determine suitability when all of the following criteria apply: patient(s) have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; the potential patient benefit justifies the potential risks of the treatment and the potential risks are not unreasonable in the context or condition to be treated; and the expanded use of the investigational drug for the requested treatment will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the product or otherwise compromise the potential development of the product.

There is no obligation for a sponsor to make its drug products available for expanded access; however, a sponsor must make its expanded access policy publicly available upon the earlier of initiation of a Phase 2 or Phase 3 clinical trial; or 15 days after the drug or biologic receives designation as a breakthrough therapy, fast track product, or regenerative medicine advanced therapy.

Human Clinical Trials in Support of an NDA

Clinical trials involve the administration of the investigational product candidate to human subjects under the supervision of a qualified investigator in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written clinical trial protocols detailing, among other things, the objectives of the study, inclusion and exclusion criteria, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated.

Human clinical trials are typically conducted in three sequential phases, but the phases may overlap or be combined. Additional studies may also be required after approval.

Phase 1 clinical trials are initially conducted in a limited population to test the product candidate for safety, including adverse effects, dose tolerance, absorption, metabolism, distribution, excretion and pharmacodynamics in healthy humans or in patients. During Phase 1 clinical trials, information about the investigational drug product's PK and pharmacological effects may be obtained to permit the design of scientifically valid Phase 2 clinical trials.

Phase 2 clinical trials are generally conducted in a limited patient population to identify possible adverse effects and safety risks, evaluate the efficacy of the product candidate for specific targeted indications and determine dose tolerance and optimal dosage. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more costly Phase 3 clinical trials. Phase 2 clinical trials are well controlled, closely monitored and conducted in a limited patient population.

Phase 3 clinical trials proceed if the Phase 2 clinical trials demonstrate that a dose range of the product candidate is potentially effective and has an acceptable safety profile. Phase 3 clinical trials are undertaken within an expanded patient population to further evaluate dosage, provide substantial evidence of clinical efficacy and further test for safety in an expanded and diverse patient population at multiple, geographically dispersed clinical trial sites. A well-controlled, statistically robust Phase 3 clinical trial that is designed to deliver the data that regulatory authorities will use to decide whether or not to approve, and, if approved, how to appropriately label a drug, is referred to as "pivotal."

In some cases, the FDA may approve an NDA for a product candidate but require the sponsor to conduct additional clinical trials to further assess the product candidate's safety and effectiveness after approval. Such post-approval trials are typically referred to as Phase 4 clinical trials. These studies are used to gain additional experience from the treatment of a larger number of patients in the intended treatment group.

IND annual reports detailing, among other things, the results of the clinical trials must be submitted to the FDA and IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the product; and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

Concurrent with clinical trials, companies often complete additional animal studies. They must also develop additional information about the chemistry and physical characteristics of the drug as well as 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 drug candidate and, among other things, must develop methods for testing the identity, strength, quality, purity, and potency of the final drug. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

Pediatric Studies

Under the Pediatric Research Equity Act of 2003, or PREA, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Sponsors must also submit pediatric study plans that contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests and other information required by regulation. The applicant, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or grant full or partial waivers from the pediatric data requirements. The FDA maintains a list of diseases that are exempt from the requirements of PREA, due to low prevalence of disease in the pediatric population, and product candidates that have received orphan drug designation are generally exempt from PREA requirements, although orphan-designated drugs intended for treatment of certain molecularly targeted cancer indications are not eligible for the exemption.

Review and Approval of an NDA

In order to obtain approval to market a drug product in the United States, a marketing application must be submitted to the FDA that provides sufficient data establishing the safety and effectiveness of the proposed drug product for its intended indication. The application includes all relevant data available from pertinent preclinical and clinical trials, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls and proposed labeling, among other things. Data can come from company-sponsored clinical trials intended to test the safety and effectiveness of a use of a product, or from a number of alternative sources, including studies initiated by independent investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety, purity and potency of the drug product to the satisfaction of the FDA.

The NDA is a vehicle through which applicants formally propose that the FDA approve a new drug product for marketing and sale in the United States for one or more indications. Every new non-biologic drug product candidate must be the subject of an approved NDA before it may be commercialized in the United States. BLAs are submitted for approval of biologic products. Under federal law, the submission of most NDAs is subject to an application user fee. The sponsor of an approved NDA is also subject to an annual program fee. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for products with orphan designation, an exception from the program fee when the program does not engage in manufacturing the drug during a particular fiscal year and a waiver for certain small businesses.

The FDA conducts a preliminary review of the application, generally within 60 calendar days of its receipt, and strives to inform the sponsor within 74 days whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept the application for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Under certain circumstances, the FDA may determine the application is not sufficiently complete to permit a substantive review and will issue a refuse to file letter. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs. Under that agreement, 90% of applications seeking approval of New Molecular Entities, or NMEs, are meant to be reviewed within ten months from the date on which the FDA accepts the application for filing, and 90% of applications for NMEs that have been designated for Priority Review are meant to be reviewed within six months of the filing date. The review process and the Prescription Drug User Fee Act, or PDUFA, goal date may be extended by the FDA to consider new information or clarification provided by the applicant, to address a deficiency identified by the FDA in the original submission, or for other reasons.

Before approving an application, the FDA typically will inspect the facility or facilities where the product is being or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA submission, including component manufacturing, finished product manufacturing and control testing laboratories. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP.

The FDA may refer an application for a novel product to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that review, evaluate and provide a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but the FDA considers such recommendations carefully when making decisions.

Fast Track, Breakthrough Therapy, Priority Review

The FDA has certain programs designed to expedite the development and review of product candidates intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs include Fast Track designation, Breakthrough Therapy designation, Priority Review designation and Regenerative Medicine Advanced Therapy designation. Sponsors must request these designations at appropriate points in the development process.

The FDA may designate a product for Fast Track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition and it demonstrates the potential to address unmet medical needs for such a disease or condition. For Fast Track products, sponsors may have greater interaction with the FDA, and the FDA may initiate review of sections of a Fast Track product's application before the application is complete, in a process called rolling review. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information, and the sponsor must pay applicable user fees. However, the FDA's PDUFA goal for reviewing a Fast Track application does not begin until the last section of the application is submitted. In addition, the Fast Track designation may be withdrawn if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process or for the other reasons.

A product may be designated as a Breakthrough Therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. A product that receives Breakthrough Therapy Designation is eligible for all of the features of Fast Track Designation, and additionally is eligible for intensive guidance throughout the development process and a commitment to involve senior staff.

The FDA may designate a product for Priority Review if it treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A Priority Review designation is intended to direct overall attention and resources to the evaluation of such applications and to shorten the FDA's goal for taking action on a marketing application from ten months to six months.

Accelerated Approval Pathway

The FDA may grant accelerated approval to a product for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on IMM or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. Products granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, efficacy biomarker or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints.

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a product, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. The benefit of accelerated approval derives from the potential to receive approval based on surrogate endpoints sooner than possible for trials with clinical or survival endpoints, rather than deriving from any explicit shortening of the FDA approval timeline, as is the case with Priority Review.

The accelerated approval pathway is contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the product's clinical benefit. As a result, a product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Under the Food and Drug Omnibus Reform Act of 2022, or FDORA, the FDA is now permitted to require, as appropriate, that such trials be underway prior to approval or within a specific time period after the date accelerated approval is granted. Under FDORA, the FDA has increased authority for expedited procedures to withdraw approval of the product if, for example, the confirmatory trial fails to verify the predicted clinical benefit of the product. In addition, the FDA generally requires, unless otherwise informed by the agency, pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product.

The FDA's Decision on an NDA

On the basis of the FDA's evaluation of the application and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a new product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, or require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess the drug's safety after approval. The agency may also require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including Risk Evaluation and Mitigation Strategies (REMS), to help ensure that the benefits of the product outweigh the potential risks. REMS programs can include medication guides, communication plans for health care professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring and the use of patent registries. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. The FDA may require a REMS before or after approval if it becomes aware of a serious risk associated with use of the product. The requirement for a REMS can materially affect the potential market and profitability of a product. After approval, many types of changes to the approved product, such as adding new indications, changing manufacturing processes and adding labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Regulation

A sponsor that obtains regulatory approval for marketing of a new product or a new indication for an existing product, will be subject to numerous post-approval regulatory requirements. The sponsor will be required to report, among other things, certain adverse reactions and manufacturing problems to the FDA, provide updated safety and efficacy information, comply with requirements concerning advertising and promotional labeling requirements, and submit NDA annual reports. Manufacturers and certain of their subcontractors, including those supplying products, ingredients and components, 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 ongoing regulatory requirements, including cGMP regulations, which impose certain procedural and documentation requirements upon manufacturers. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. Accordingly, the sponsor and its third-party manufacturers must continue to expend time, money and effort to maintain compliance with cGMP regulations and other regulatory requirements.

The FDA may withdraw approval if compliance with regulatory requirements is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, may result in revisions to the approved labeling to add new safety information, requirements for post-market studies or clinical trials to assess safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences may include:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;

•refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product license approvals;

•product seizure or detention, or refusal to permit the import or export of products; or

•injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates the marketing, labeling, advertising and promotion of prescription drug products placed on the market. This regulation includes, among other things, standards and regulations for direct-to-consumer advertising, communications regarding unapproved uses, industry-sponsored scientific and educational activities, and promotional activities involving the Internet and social media. Promotional claims about a drug's safety or effectiveness are prohibited before the drug is approved. After approval, a drug product generally may not be promoted for uses that are not approved by the FDA, as reflected in the product's prescribing information. In the United States, health care professionals are generally permitted to prescribe drugs for such uses not described in the drug's labeling, known as off-label uses, because the FDA does not regulate the practice of medicine. However, FDA regulations impose rigorous restrictions on manufacturers' communications, prohibiting the promotion of off-label uses. It may be permissible, under very specific conditions, for a manufacturer to engage in nonpromotional, non-misleading communication regarding off-label information, such as distributing scientific or medical journal information.

If a company is found to have promoted off-label uses, it may become subject to administrative and judicial enforcement by the FDA, the Department of Justice, or the DOJ, or the Office of the Inspector General of the Department of Health and Human Services, as well as state authorities. This could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that materially restrict the manner in which a company promotes or distributes drug products. The federal government has levied large civil and criminal fines against companies for alleged improper promotion, and has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed.

In addition, manufacturers and other parties involved in the drug supply chain for prescription drug products must comply with product tracking and tracing requirements and for notify the FDA of counterfeit, diverted, stolen and intentionally adulterated products or products that are otherwise unfit for distribution in the United States.

Section 505(b)(2) NDAs

NDAs for most new drug products are based on two full clinical studies which must contain substantial evidence of the safety and efficacy of the proposed new product for the proposed use. These applications are submitted under Section 505(b)(1) of the FDCA. The FDA is, however, authorized to approve an alternative type of NDA under Section 505(b)(2) of the FDCA. This type of application allows the applicant to rely, in part, on the FDA's previous findings of safety and efficacy or literature for a previously approved drug product, also known as a listed drug. Specifically, Section 505(b)(2) applies to NDAs for which certain investigations made to show whether or not the drug is safe and effective "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted."

NDAs filed under Section 505(b)(2) provide an alternate and potentially more expeditious pathway to FDA approval for new or improved formulations or new uses of previously approved products. If the 505(b)(2) applicant can establish that reliance on the FDA's previous approval is scientifically appropriate, the applicant may eliminate the need to conduct certain preclinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements to support the change from the approved product. The FDA may then approve the new drug candidate for all or some of the label indications for which the listed drug has been approved, subject to any regulatory exclusivities or patents for the listed drug (as further described below), as well as for any new indication or use sought by the Section 505(b)(2) applicant.

Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, Congress established an abbreviated regulatory scheme authorizing the FDA to approve generic drugs that are shown to contain the same active ingredients as, and to be bioequivalent to, drugs previously approved by the FDA pursuant to NDAs, known as the reference listed drugs, or RLDs. Abbreviated new drug applications, or ANDAs, generally do not include preclinical and clinical data to demonstrate safety and effectiveness. Instead, the applicant must provide information and data showing that its proposed generic version is identical to the RLD with respect to the active ingredients, route of administration, dosage form, strength and conditions of use of the drug. The FDA must also determine whether the generic drug is bioequivalent to the RLD. Under the statute, a generic drug is bioequivalent to a RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug." Upon approval of an ANDA, the FDA indicates whether the

generic product is "therapeutically equivalent" to the RLD in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Depending on state laws, generic drugs that are found to be therapeutically equivalent may be automatically substituted for prescriptions for the RLD by the dispensing pharmacist, without the intervention of the prescriber.

Under the Hatch-Waxman Amendments, the FDA may not approve an ANDA until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity. For the purposes of this provision, a new chemical entity, or NCE, is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such NCE exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval.

Hatch-Waxman Patent Certification and the 30-Month Stay

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant's product or an approved method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. When an ANDA applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any relevant patents listed for the approved product in the Orange Book in the same manner as an ANDA applicant.

Specifically, the applicant must certify with respect to each patent that:

•the required patent information has not been filed;

•the listed patent has expired;

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

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

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents, the application will not be approved until all the listed patents claiming the referenced product have expired (other than method of use patents involving indications for which the applicant is not seeking approval).

If the ANDA or Section 505(b)(2) NDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the application has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV notice. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA or 505(b)(2) application until the earlier of 30 months after the receipt of the Paragraph IV notice, the expiration of the patent, or a decision in the infringement case that is favorable to the ANDA applicant.

As a result, approval of a Section 505(b)(2) NDA or ANDA may be delayed until all the listed patents claiming the referenced product have expired, until any non-patent exclusivity, such as exclusivity for obtaining approval of a new chemical entity, listed in the Orange Book for the referenced product has expired, or, in the case of a Paragraph IV certification and subsequent patent infringement suit, until the earlier of 30 months, settlement of the lawsuit or a decision in the infringement case that is favorable to the applicant.

Pediatric Exclusivity

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of an existing regulatory exclusivity or certain patents. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted.

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may designate a drug product as an "orphan drug" if it is intended to treat a rare disease or condition, generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a product available in the United States for treatment of the disease or condition will be recovered from sales of the product. A company must seek orphan drug designation before submitting an NDA for the candidate product. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan drug designation does not shorten the PDUFA goal dates for the regulatory review and approval process, although it does convey certain advantages such as tax benefits and exemption from the PDUFA application fee.

If a product with orphan designation receives the first FDA approval for the disease or condition for which it has such designation or for an indication or use within the rare disease or condition for which it was designated, the product generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor's marketing application for the same drug for the same condition for seven years, except in certain limited circumstances. Orphan exclusivity does not block the approval of a different product for the same rare disease or condition, nor does it block the approval of the same product for different conditions. If a drug designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity.

Orphan drug exclusivity also may not bar approval of another product under certain specified circumstances, including if a subsequent product with the same drug for the same condition is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand.

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during the FDA regulatory review. The restoration period granted on a patent covering a product is typically one-half the time between the effective date of an IND and the submission date of an application, plus the time between the submission date of an application and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved product is eligible for the extension, and only those claims covering the approved product, a method for using it, or a method for manufacturing it may be extended. Additionally, the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. The United States Patent and Trademark Office reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Health Care Law and Regulation

Health care providers and third-party payors play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with providers, consultants, third-party payors and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, patient privacy laws and regulations and other health care laws and regulations that may constrain business and/or financial arrangements. Restrictions under applicable federal and state health care laws and regulations, include the following:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal health care program such as Medicare and Medicaid. A person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation;

•the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious or fraudulent or knowingly making, using or causing to made or used a false record or statement to avoid, decrease or conceal an obligation to pay money to the federal government. Manufacturers can be held liable under the federal False Claims Act even when they do not submit claims directly to government payors if they are deemed to "cause" the submission of false or fraudulent claims. The federal False Claims Act also permits a private individual acting as a "whistleblower" to bring actions on behalf of the federal government alleging violations of the federal False Claims Act and to share in any monetary recovery;

•the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal laws that prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any health care benefit program or making false statements relating to health care matters; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

•HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In addition, there may be additional federal, state and non-U.S. laws which govern the privacy and security of health and other personal information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts;

•the federal false statements statute, which prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for health care benefits, items or services;

•the Foreign Corrupt Practices Act, or FCPA, which prohibits companies and their intermediaries from making, or offering or promising to make improper payments to non-U.S. officials for the purpose of obtaining or retaining business or otherwise seeking favorable treatment;

•the federal transparency requirements known as the federal Physician Payments Sunshine Act, under the Patient Protection and Affordable Care Act, as amended by the Health Care Education Reconciliation Act, or the ACA, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the United States Department of Health and Human Services, information related to payments and other transfers of value made by that entity to physicians, certain other licensed healthcare practitioners and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members;

•federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs;

•federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers; and

•analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to health care items or services that are reimbursed by non-government third-party payors, including private insurers.

Further, some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures. Additionally, some state and local laws require the registration of pharmaceutical sales representatives in the jurisdiction.

State laws also govern the privacy and security of personal information, including health information. Many state laws differ from each other in various ways, thus complicating compliance efforts. For example, the California Consumer Protection Act, or CCPA, establishes data privacy rights for individuals located in California and imposes certain requirements on how businesses can collect and use personal information about such individuals. The California Privacy Rights Act, or CPRA, which became effective on January 1, 2023, imposes additional obligations on companies covered by the legislation and significantly modifies the CCPA, including by expanding consumers' rights with respect to certain

sensitive personal information, and establishes a state agency vested with the authority to enforce the CCPA. The CCPA catalyzed the enactment of similar, comprehensive privacy and data protection legislation in several other U.S. states, which became effective over the past couple of years, including in Virginia, Colorado, Utah, Connecticut, Montana, Oregon, Texas, Delaware, Iowa, New Hampshire, Nebraska and New Jersey. Other U.S. states have either passed or have proposed similar privacy and data protection legislation. Washington state's My Health My Data Act, which entered into force on March 31, 2024, expands the definition of consumer health data, affords consumers with privacy rights and creates a private right of action, which could generate litigation. Although many of the existing state privacy laws exempt clinical trial information and health information governed by HIPAA, future privacy and data protection laws may be broader in scope and apply to our business. Further, data privacy and security laws and regulations in foreign jurisdictions, such as the EU's General Data Protection Regulation, or EU GDPR, and the United Kingdom's implementation of the same, may impose additional obligations on the collection, use and other processing of personal information, which may be more stringent or different than those in the United States.

Regulators and legislators in the U.S. are increasingly scrutinizing and restricting certain personal data transfers and transactions involving foreign countries. For example, the December 2024 executive order Preventing Access to Americans' Bulk Sensitive Personal Data and United States Government-Related Data by Countries of Concern as implemented by Department of Justice regulations, prohibits data brokerage transactions involving certain sensitive personal data categories, including health data, genetic data, and biospecimens, to countries of concern, including China. The regulations also restrict certain investment agreements, employment agreements and vendor agreements involving such data and countries of concern, absent specified cybersecurity controls. Actual or alleged violations of these regulations may be punishable by criminal and/or civil sanctions, and may result in exclusion from participation in federal and state programs.

Pharmaceutical Insurance Coverage and Health Care Reform

In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated health care costs. Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Thus, even if a product candidate is approved, sales of the product will depend, in part, on the extent to which third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations, provide coverage and establish adequate reimbursement levels 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 price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable marketing approvals. Nonetheless, product candidates may not be considered medically necessary or cost effective. A decision by a third-party payor not to cover a product could reduce physician utilization once the product is approved and have a material adverse effect on sales, results of operations and financial condition. Additionally, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payor to payor.

The containment of health care costs also has become a priority of federal, state and foreign governments and the prices of products have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit a company's revenue generated from the sale of any approved products. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive marketing approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs and biologics and other medical products, government control and other changes to the health care system in the United States.

In 2010, the United States Congress enacted the ACA, which, among other things, included changes to the coverage and payment for drug products under government health care programs. Among the provisions of the ACA of importance to our potential product candidates are:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;
- expansion of eligibility criteria for Medicaid programs, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program;
- expanded the types of entities eligible for the 340B drug discount program;
- established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 70% point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D (later replaced effective January 1, 2025 with the Medicare Part D Manufacturer Discount Program); and
- a Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. The Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. This includes aggregate reductions of Medicare payments to providers up to 2% per fiscal year. Subsequent legislation extended the 2% which remains in effect through 2031. The American Taxpayer Relief Act of 2012 further reduced Medicare payments to several types of providers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Due to the Statutory Pay-As-You-Go Act of 2010, estimated budget deficit increases resulting from the American Rescue Plan Act of 2021, and subsequent legislation, Medicare payments to providers will be further reduced starting in 2025 absent further legislation. These laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Other legislative changes since the ACA was enacted include the American Rescue Plan Act of 2021, effective January 1, 2024, under which Medicaid statutory rebates are no longer capped at 100% of AMP (average manufacturer price).

The Inflation Reduction Act of 2022, or IRA, includes several provisions that may impact our business to varying degrees, including provisions that reduce the out-of-pocket cap for Medicare Part D beneficiaries to $2,000 starting in 2025; impose new manufacturer financial liability on certain drugs under Medicare Part D, allow the U.S. government to negotiate Medicare Part B and Part D price caps for certain high-cost drugs and biologics without generic or biosimilar competition, require companies to pay rebates to Medicare for certain drug prices that increase faster than inflation, and delay the rebate rule that would limit the fees that pharmacy benefit managers can charge. Further, under the IRA, orphan drugs are exempted from the Medicare drug price negotiation program, but only if they have one orphan designation and for which the only approved indication is for that disease or condition. If a product receives multiple orphan designations or has multiple approved indications, it may not qualify for the orphan drug exemption. The implementation of the IRA is currently subject to ongoing litigation challenging the constitutionality of the IRA's Medicare drug price negotiation program. The effects of the IRA on our business and the healthcare industry in general are not yet known.

The costs of prescription pharmaceuticals have also been the subject of considerable discussion in the United States. To date, there have been several recent U.S. congressional inquiries, as well as proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. Numerous executive orders designed to reduce prescription drug costs have been issued and may be issued in the future. Although a number of these and other proposed measures may require authorization through additional legislation to become effective, and the sitting presidential administration may reverse or otherwise change these measures, it is expected that the presidential administration and Congress will continue to seek new measures to control drug costs.

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the

ultimate demand for our products, once approved, or put pressure on our product pricing. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

Review and Approval of Medicinal Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, an applicant will need to obtain the necessary approvals by the comparable non-U.S. regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. The approval process ultimately varies between countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others. Specifically, however, the process governing approval of medicinal products in the European Union, or EU, generally follows the same lines as in the United States. It entails satisfactory completion of preclinical studies and adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each proposed indication. It also requires the submission to the relevant competent authorities of a marketing authorization application, or MAA, and granting of a marketing authorization by these authorities before the product can be marketed and sold in the EU.

Clinical Trial Approval

In April 2014, the EU adopted the Clinical Trials Regulation, (EU) No 536/2014, which replaced the Clinical Trials Directive 2001/20/EC on January 31, 2022. The Clinical Trials Regulation is directly applicable in all EU Member States meaning no national implementing legislation in each EU Member State is required. The Clinical Trials Regulation aims to simplify and streamline the approval of clinical trials in the EU. Under the new coordinated procedure for the approval of clinical trials, the sponsor of a clinical trial is required to submit a single application for approval of a clinical trial to a reporting EU Member State through the EU portal known as the Clinical Trials Information System, or CTIS. The submission procedure is the same irrespective of whether the clinical trial is to be conducted in a single EU Member State or in more than one EU Member State.

PRIME Designation in the EU

In March 2016, the EMA launched an initiative to facilitate development of product candidates in indications, often rare, for which few or no therapies currently exist. The Priority Medicines, or PRIME, scheme is intended to encourage drug development in areas of unmet medical need and provides accelerated assessment of products representing substantial innovation where the marketing authorization application, or MAA, will be made through the centralized procedure. Eligible products must target conditions for which there is an unmet medical need (there is no satisfactory method of diagnosis, prevention or treatment in the EU or, if there is, the new medicine will bring a major therapeutic advantage) and they must demonstrate the potential to address the unmet medical need. Products from small- and medium-sized enterprises, or SMEs, may qualify for earlier entry into the PRIME scheme than larger companies. Many benefits accrue to sponsors of product candidates with PRIME designation, including but not limited to, early and proactive regulatory dialogue with the EMA, frequent discussions on clinical trial designs and other development program elements, and accelerated MAA assessment once a dossier has been submitted. Importantly, a dedicated EMA contact and rapporteur from the Committee for Medicinal Products for Human Use, or CHMP, or Committee for Advanced Therapies, are appointed early in the PRIME scheme; facilitating increased understanding of the product at the EMA's committee level. A kick-off meeting initiates these relationships and includes a team of multidisciplinary experts at the EMA to provide guidance on the overall development and regulatory strategies. Where, during the course of development, a medicine no longer meets the eligibility criteria, support under the PRIME scheme may be withdrawn.

Marketing Authorization

To obtain a marketing authorization for a product under EU regulatory systems, an applicant must submit an MAA either under a centralized procedure administered by the EMA, or one of the procedures administered by competent authorities in the EU Member States (decentralized procedure, national procedure or mutual recognition procedure). A marketing authorization may be granted only to an applicant established in the EU.

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid throughout the EU, and in the additional Member States of the European Economic Area: Iceland, Liechtenstein and Norway. Pursuant to Regulation (EC) No 726/2004, the centralized procedure is compulsory for specific products, including

for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy medicinal products (gene-therapy, somatic cell-therapy or tissue-engineered medicines), and products with a new active substance indicated for the treatment of HIV, AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and other immune dysfunctions, and viral diseases. The centralized procedure is optional for products containing a new active substance not yet authorized in the EU, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU. We anticipate that the centralized procedure will be mandatory for the product candidates we are developing.

Under the centralized procedure, the CHMP is responsible for conducting the initial assessment of a product and for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the EU, the maximum timeframe for the evaluation of an MAA by the EMA is 210 days, excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the CHMP. Clock stops may extend the timeframe of evaluation of an MAA considerably beyond 210 days. Where the CHMP gives a positive opinion, it provides the opinion together with supporting documentation to the European Commission, who makes the final decision to grant a marketing authorization, which is issued within 67 days of receipt of the EMA's recommendation. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. If the CHMP accepts such request, the time limit of 210 days will be reduced to 150 days, excluding clock stops, but it is possible that the CHMP can revert to the standard time limit for the centralized procedure if it considers that it is no longer appropriate to conduct an accelerated assessment.

The European Commission may grant a so-called "marketing authorization under exceptional circumstances". Such authorization is intended for products for which the applicant can demonstrate that it is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or in the present state of scientific knowledge, comprehensive information cannot be provided, or it would be contrary to generally accepted principles of medical ethics to collect such information. Consequently, a marketing authorization under exceptional circumstances may be granted subject to certain specific obligations, which may include the following:

- the applicant must complete an identified program of studies within a time period specified by the competent authority, the results of which form the basis of a reassessment of the benefit/risk profile;
- the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radiopharmaceutical, by an authorized person; and
- the package leaflet and any medical information must draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

A marketing authorization under exceptional circumstances is subject to annual review to reassess the risk-benefit balance in an annual reassessment procedure. Continuation of the authorization is linked to the annual reassessment and a negative assessment could potentially result in the marketing authorization being suspended or revoked. The renewal of a marketing authorization of a medicinal product under exceptional circumstances, however, follows the same rules as a "normal" marketing authorization. Thus, a marketing authorization under exceptional circumstances is granted for an initial five years, after which the authorization will become valid indefinitely, unless the EMA decides that safety grounds merit one additional five-year renewal.

The European Commission may also grant a so-called "conditional marketing authorization" prior to obtaining the comprehensive clinical data required for an application for a full marketing authorization. Such conditional marketing authorizations may be granted for product candidates intended for treating, preventing or diagnosing seriously debilitating or life-threatening diseases (including medicines designated as orphan medicinal products), if (i) the risk-benefit balance of the product candidate is positive, (ii) it is likely that the applicant will be in a position to provide the required comprehensive clinical trial data post-authorization, (iii) the product fulfills an unmet medical need and (iv) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required. A conditional marketing authorization may contain specific obligations to be fulfilled by the marketing authorization holder, including obligations with respect to the completion of ongoing or new studies, and with respect to the collection of pharmacovigilance data. Conditional marketing authorizations are valid for one year, and may be renewed annually, if the risk-benefit balance remains positive, and after an assessment of the need for additional or modified conditions and/or specific obligations. The timelines for the centralized procedure described above also apply with respect to the review by the CHMP of applications for a conditional marketing authorization. A conditional marketing authorization can be converted into a standard centralized marketing authorization (no longer subject to specific obligations) once the marketing authorization holder fulfils the obligations imposed and the complete data confirm that the medicine's benefits continue to outweigh its risks.

The EU medicines rules expressly permit the EU Member States to adopt national legislation prohibiting or restricting the sale, supply or use of any medicinal product containing, consisting of or derived from a specific type of human or animal cell, such as embryonic stem cells. While the products we have in development do not make use of embryonic stem cells, it is possible that the national laws in certain EU Member States may prohibit or restrict us from commercializing our products, even if they have been granted an EU marketing authorization.

Unlike the centralized authorization procedure, the decentralized marketing authorization procedure requires a separate application to, and leads to separate approval by, the competent authorities of each EU Member State in which the product is to be marketed. This application is identical to the application that would be submitted to the EMA for authorization through the centralized procedure. The reference EU Member State prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. The resulting assessment report is submitted to the concerned EU Member States who, within 90 days of receipt, must decide whether to approve the assessment report and related materials. If a concerned EU Member State cannot approve the assessment report and related materials due to concerns relating to a potential serious risk to public health, disputed elements may be referred to the European Commission, whose decision is binding on all EU Member States.

The mutual recognition procedure similarly is based on the acceptance by the competent authorities of the EU Member States of the marketing authorization of a medicinal product by the competent authorities of other EU Member States. The holder of a national marketing authorization may submit an application to the competent authority of an EU Member State requesting that this authority recognize the marketing authorization delivered by the competent authority of another EU Member State.

Data and Market Exclusivity

In the EU, innovative medicinal products approved on the basis of a complete and independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Directive 2001/83/EC. Regulation (EC) No 726/2004 repeats this entitlement for medicinal products authorized in accordance the centralized authorization procedure. Data exclusivity prevents applicants for authorization of generics or biosimilars of these innovative products from referencing the innovator's pre-clinical and clinical trial data contained in the dossier of the reference product when applying for a generic or biosimilar marketing authorization in the EU, during a period of eight years from the date on which the reference product was first authorized in the EU. During an additional two-year period of market exclusivity, a generic or biosimilar MAA can be submitted and authorized, and the innovator's data may be referenced, but no generic or biosimilar medicinal product can be placed on the EU market until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. There is no guarantee that a product will be considered by the EMA to be an innovative medicinal product, and products may not qualify for data exclusivity. Even if a product is considered to be an innovative medicinal product so that the innovator gains the prescribed period of data exclusivity, another company nevertheless could also market another version of the product if such company obtained marketing authorization based on an MAA with a complete and independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Periods of Authorization and Renewals

A marketing authorization has an initial validity for five years in principle. The marketing authorization may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the EMA or by the competent authority of the EU Member State for a nationally authorized product. Once subsequently definitively renewed, the marketing authorization shall be valid for an unlimited period, unless the European Commission or the national competent authority decides, on justified grounds relating to pharmacovigilance, to require one additional five-year renewal period. Any authorization which is not followed by the actual placing of the medicinal product on the EU market (in the case of the centralized procedure) or on the market of the authorizing EU Member State for a nationally authorized product within three years after authorization ceases to be valid (the so-called sunset clause).

Paediatric Studies and Exclusivity

Prior to obtaining a marketing authorization in the EU, applicants must demonstrate compliance with all measures included in an EMA-approved pediatric investigation plan, or PIP, covering all subsets of the pediatric population, unless the EMA has granted a product-specific waiver, a class waiver, or a deferral for one or more of the measures included in the PIP. The respective requirements for all marketing authorization procedures are laid down in Regulation (EC) No 1901/2006, the so-called Pediatric Regulation. This requirement also applies when a company wants to add a new indication, pharmaceutical form or route of administration for a medicine that is already authorized. The Paediatric Committee of the EMA, or PDCO, may grant deferrals for some medicines, allowing a company to delay development of the medicine for children until there is enough information to demonstrate its effectiveness and safety in adults. The PDCO may also grant waivers when

development of a medicine for children is not needed or is not appropriate, such as for diseases that only affect the elderly population. Before an MAA can be filed, or an existing marketing authorization can be amended, the EMA determines that companies actually comply with the agreed studies and measures listed in each relevant PIP. If an applicant obtains a marketing authorization in all EU Member States, or a marketing authorization granted in the centralized procedure by the European Commission, and the study results for the population are included in the product information, even when negative, the medicine is then eligible for an additional six-month period of qualifying patent protection through extension of the term of the Supplementary Protection Certificate or SPC, provided an application for such extension is made at the same time as filing the SPC application for the product, or at any point up to two years before the SPC expires. The incentive in the case of orphan medicinal products is that a two year extension of the orphan market exclusivity may be available. This pediatric reward is subject to specific conditions and is not automatically available when data in compliance with the PIP are developed and submitted.

Orphan Designation and Exclusivity

Products receiving orphan designation in the EU can receive ten years of market exclusivity, during which time no "similar medicinal product" may be placed on the market. A "similar medicinal product" is defined as a medicinal product containing a similar active substance or substances as contained in an authorized orphan medicinal product, and which is intended for the same therapeutic indication.

Regulation (EC) No. 141/2000, as implemented by Regulation (EC) No. 847/2000 provides that a product can be designated as an orphan product by the European Commission if its sponsor can establish: (1) that the product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; (2) either (a) such condition affects no more than five (5) in ten thousand (10,000) persons in the EU when the application is made, or (b) it is unlikely that the product, without the benefits derived from orphan status, would generate sufficient return in the EU to justify the necessary investment in its development; and (3)there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the EU or, if such method exists, the product will be of significant benefit to those affected by that condition. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers. The application for orphan designation must be submitted before the application for marketing authorization. The applicant will receive a fee reduction for the MAA if the orphan designation has been granted, but not if the designation is still pending at the time the marketing authorization is submitted. Orphan designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

However, a marketing authorization may be granted to a similar medicinal product with the same orphan indication during the ten-year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if this product is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity.

Regulatory Requirements After a Marketing Authorization has been Obtained

If an authorization for a medicinal product in the EU is obtained, the holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. These include:

- Compliance with the EU's stringent pharmacovigilance or safety reporting rules must be ensured. These rules can impose post-authorization studies and additional monitoring obligations.

- The manufacturing of authorized medicinal products, for which a separate manufacturer's license is mandatory, must also be conducted in strict compliance with the applicable EU laws, regulations and guidance, including Directive 2001/83/EC, Directive (EU) 2017/1572, Regulation (EC) No 726/2004 and the European Commission Guidelines for Good Manufacturing Practice. These requirements include compliance with EU cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients, including the manufacture of active pharmaceutical ingredients outside of the EU with the intention to import the active pharmaceutical ingredients into the EU.

- The marketing and promotion of authorized drugs, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs and/or the general public, are strictly regulated in the EU. Direct-to-consumer advertising of prescription medicines is prohibited across the EU.

All of the aforementioned EU rules are generally applicable in the European Economic Area, or EEA, which consists of the EU Member States, plus Norway, Liechtenstein and Iceland.

Reform of the Regulatory Framework in the European Union

The European Commission introduced legislative proposals in April 2023 that, if implemented, will replace the current regulatory framework in the EU for all medicines (including those for rare diseases and for children). The European Commission has provided the legislative proposals to the European Parliament and the European Council for their review and approval, and, in April 2024, the European Parliament proposed amendments to the legislative proposals. Once the European Commission's legislative proposals are approved (with or without amendment), they will be adopted into EU law.

Pricing Decisions for Approved Products

In the EU, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost- effectiveness of a particular product candidate to currently available therapies or so-called health technology assessments, in order to obtain reimbursement or pricing approval. For example, EU Member States have the option to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. EU Member States may approve a specific price for a product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other EU Member States allow companies to fix their own prices for products, but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the EU have increased the amount of discounts required on pharmaceuticals and these efforts could continue as countries attempt to manage health care expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the EU. The downward pressure on health care costs in general, particularly prescription products, has become intense.

As a result, increasingly high barriers are being erected to the entry of new products. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various EU Member States, and parallel trade, i.e., arbitrage between low-priced and high-priced EU Member States, can further reduce prices.

Special pricing and reimbursement rules may apply to orphan products. Inclusion of orphan products in reimbursement systems tend to focus on the medical usefulness, need, quality and economic benefits to patients and the healthcare system as for any drug. Acceptance of any medicinal product for reimbursement may come with cost, use and often volume restrictions, which again can vary by country. In addition, results-based rules of reimbursement may apply. 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 products, if approved in those countries.

The delivery of healthcare in the EU, including the establishment and operation of health services and the pricing and reimbursement of medicines, is almost exclusively a matter for national, rather than EU, law and policy. National governments and health service providers have different priorities and approaches to the delivery of healthcare and the pricing and reimbursement of products in that context. In general, however, the healthcare budgetary constraints in most EU Member States have resulted in restrictions on the pricing and reimbursement of medicines by relevant health service providers.

General Data Protection Regulation

The collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the EU, including personal health data, is subject to the EU GDPR, which became effective on May 25, 2018. Following the United Kingdom's, or UK's, withdrawal from the EU, or Brexit, the EU GDPR has been incorporated into UK laws, or UK GDPR (together with the EU GDPR, GDPR). The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, ensuring certain accountability measures are in place and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the EU and the UK, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million (£17.5 million) or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR is a rigorous and time-intensive process that may increase the cost of doing business or require companies to change their business practices to ensure full compliance.

Brexit and the Regulatory Framework in the United Kingdom

The United Kingdom formally left the EU on January 31, 2020, and the EU and the United Kingdom have concluded a trade and cooperation agreement, or TCA, which was provisionally applicable since January 1, 2021 and has been formally applicable since May 1, 2021. The TCA includes specific provisions concerning pharmaceuticals, which include the mutual recognition of GMP, inspections of manufacturing facilities for medicinal products and GMP documents issued, but does not provide for wholesale mutual recognition of UK and EU pharmaceutical regulations. At present, the United Kingdom has implemented EU legislation on the marketing, promotion and sale of medicinal products through the Human Medicines Regulations 2012 (as amended). Except in respect of the EU Clinical Trials Regulation, the regulatory regime in the UK therefore currently largely aligns with EU regulations, however it is possible that these regimes will diverge more significantly in future now that the UK's regulatory system is independent from the EU and the TCA does not provide for mutual recognition of UK and EU pharmaceutical legislation. However, notwithstanding that there is no wholesale recognition of EU pharmaceutical legislation under the TCA, under a new international recognition procedure that was put in place by the Medicines and Healthcare products Regulatory Agency, or MHRA, on January 1, 2024, the MHRA may take into account decisions on the approval of a marketing authorization from the EMA (and certain other regulators) when considering an application for a UK marketing authorization.

On February 27, 2023, the UK government and the European Commission announced a political agreement in principle to replace the Northern Ireland Protocol with a new set of arrangements, known as the "Windsor Framework". The Windsor Framework was approved by the EU-UK Joint Committee on March 24, 2023, and the medicines aspects of the Windsor Framework have applied since January 1, 2025. This new framework fundamentally changes the previous system under the Northern Ireland Protocol, including with respect to the regulation of medicinal products in the United Kingdom. In particular, the MHRA is now responsible for approving all medicinal products destined for the UK market (i.e., Great Britain and Northern Ireland), and the EMA no longer has any role in approving medicinal products destined for Northern Ireland under the centralized procedure. A single UK-wide marketing authorization will be granted by the MHRA for all novel medicinal products to be sold in the UK, enabling products to be sold in a single pack and under a single authorization throughout the UK. In addition, the new arrangements require all medicines placed on the UK market to be labelled "UK only", indicating they are not for sale in the EU.

Despite Brexit, the EU and UK GDPR remain largely aligned. Currently, the most impactful point of divergence relates to transfer mechanisms (i.e., the ability for EU/UK companies to transfer personal information to third countries, including the United States), because it requires us to implement a variety of different contractual clauses approved by EU or UK regulators. There may be further divergence in the future, including with regard to administrative burdens. The UK has announced plans to reform the country's data protection legal framework in its Data Reform Bill, which will introduce significant changes from the EU GDPR.

Human Capital Management

Our Mission & Our Employees

We launched with a bold vision to change the course of genetically defined diseases by developing small molecules to treat them at their root cause. Our approach to drug discovery generates significant insights into disease biology and allows us to think creatively about the best way to modulate and balance gene expression. Our patient-focused product discovery approach is designed to systematically identify and validate cellular drug targets that can modulate gene expression to treat the known root cause of genetically defined diseases. We take great pride in being purposeful patient partners who do this work, not just for patients, but with patients.

We view our employees as one of our most valuable assets in serving our mission. We believe that our future success is dependent on attracting, motivating and retaining talented employees. We value the health and wellness of our employees and their families. We aim to create an equitable, inclusive and empowering work environment in which our employees can grow and advance their careers, with the overall goal of developing, expanding and retaining our workforce to support our current pipeline and future business goals. Our success also depends on our ability to attract, engage and retain a diverse group of employees.

Our Behaviors Support Our Mission

We believe success comes when we and our employees align with our mission to improve the lives of patients with genetically-defined rare diseases in areas of high unmet medical need. We are the FULcrew united around these Pillars:

- We take great pride in being Purposeful Patient Partners
- We have a culture of Trust and Transparency

•We are Invested in our People

•We have a Playful spirit and have fun together at work

•We launched Fulcrum with a Bold Scientific Vision and remain committed to this journey

Our Management of Human Capital

To effectively leverage and manage our peoples, we ensure our hiring needs are directly aligned with our strategy, we invest in our people focused on their development and journey while at Fulcrum and most importantly we identify our key talent to ensure we are focused on their retention. We track and report internally on key talent metrics including a focus on overall headcount and by function, hiring metrics, career development (promotions, etc.), turnover trends, and employee demographics (including race, gender, ethnicity). Our senior executives use these metrics to make thoughtful decisions around our people including resource planning, recruitment and retention initiatives and design of compensation and benefits programs. We share these metrics quarterly with the senior executives and board of directors to assist it in fulfilling its duties to (a) establish our enterprise compensation philosophy, (b) administer our compensation plans, (c) evaluate the performance of our executive officers and key employees and (d) review and monitor management development and succession plans.

As of February 18, 2025, we had 45 full-time employees, including a total of 13 employees with M.D. or Ph.D. degrees. Of these full-time employees, 30 employees are engaged in research and development. None of our employees are represented by labor unions or covered by collective bargaining agreements. We consider our relationship with our employees to be good.

We strongly believe in a workplace where all our employees can thrive in an inclusive environment free from discrimination, harassment, bias and prejudice. We aim to treat all individuals with respect and dignity and to provide all our employees with equal opportunity and fair treatment based on merit.

Our Compensation & Benefits

Given the highly competitive nature of our industry and the importance of recruitment and retention to our success, we strive to furnish our employees with what we believe is a very competitive and comprehensive total rewards package of compensation, benefits and services. This package includes competitive compensation, including equity compensation, and comprehensive benefits program that provides resources to help employees manage their health and well-being, finances, and life outside of work (promoting flexibility), including health insurance and dental care, vision insurance, disability insurance, paid sick leave, paid family leave, matching contributions to a 401(k) plan, employee stock purchase plan, paid time off (inclusive of vacation, holidays, focus days) and employee assistance services.

Corporate Information

Our principal executive office is located at 26 Landsdowne Street, Cambridge, MA 02139, and our telephone number is 617-651-8851. Our internet website address is www.fulcrumtx.com. The information contained on, or that can be accessed through, our website is not a part of this Annual Report on Form 10-K.

Item 1A. Risk Factors.

Our future operating results could differ materially from the results described in this Annual Report on Form 10-K due to the risks and uncertainties described below. You should consider carefully the following information about risks below in evaluating our business. If any of the following risks actually occur, our business, financial conditions, results of operations and future growth prospects would likely be materially and adversely affected. In these circumstances, the market price of our common stock would likely decline. In addition, we cannot assure investors that our assumptions and expectations will prove to be correct. Important factors could cause our actual results to differ materially from those indicated or implied by forward-looking statements. See "Cautionary Note Regarding Forward-Looking Statements" on page i of this Annual Report on Form 10-K for a discussion of some of the forward-looking statements that are qualified by these risk factors. Factors that could cause or contribute to such differences include those factors discussed below.

Risks Related to our Financial Position and Need for Additional Capital

We have incurred significant losses since our inception. We expect to incur losses over the next several years and may never achieve or maintain profitability.

Since inception, we have incurred significant operating losses. Our net loss was $9.7 million for the year ended December 31, 2024 and $97.3 million for the year ended December 31, 2023. As of December 31, 2024, we had an accumulated deficit of $519.4 million. To date, we have funded our operations primarily from the sale of shares of our capital stock and from upfront payments received under our collaboration and license agreements. We have devoted substantially all of our financial resources and efforts to research and development, including clinical trials and preclinical studies. We are still in the early stages of development of our product candidates, and we have not completed development of any product candidates. We expect to continue to incur significant expenses and operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase substantially as we:

- continue our clinical development of pociredir and any future product candidates;
- continue our ongoing preclinical studies;
- pursue the discovery of drug targets for other genetically-defined rare diseases and the subsequent development of any resulting product candidates, including for the potential treatment of inherited aplastic anemias, such as DBA, Shwachman-Diamond syndrome, and Fanconi anemia under our license agreement with CAMP4;
- seek regulatory approvals for any product candidates that successfully complete clinical trials;
- acquire or in-license products, product candidates, technologies and/or data referencing rights, such as our agreement with CAMP4;
- make any milestone payments to CAMP4 under our license agreement with CAMP4;
- maintain, expand, enforce, defend and protect our intellectual property;
- hire additional clinical, quality control and scientific personnel as needed;
- scale up our manufacturing processes and capabilities, or arrange for a third party to do so on our behalf, to support our clinical trials of any product candidate and commercialization of any of product candidates for which we may obtain marketing approval;
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain regulatory approval and that we have not out-licensed; and
- add operational, financial and management information systems and personnel, including personnel to support our product development and any future commercialization efforts, as needed, and our operations as a public company.

To become and remain profitable, we must succeed in developing, and eventually commercializing, a product or products that generate significant revenue. The ability to achieve this success will require us to be effective in a range of challenging activities, including completing preclinical testing and clinical trials of our product candidates, discovering additional product candidates, obtaining regulatory approval for these product candidates and manufacturing, marketing and selling any products for which we may obtain regulatory approval. We are only in the preliminary stages of most of these activities for our current product candidates. We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough to achieve profitability. Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability. Our expenses will increase if, among other things:

- we are required by the FDA, the EMA, or other regulatory authorities to perform trials or studies in addition to, or different than, those expected;
- there are any further delays in completing our ongoing clinical trial or otherwise in the development of any of our current or future product candidates, such as due to any further clinical holds imposed by the FDA (similar to the hold on the IND application for pociredir in SCD that was lifted in August 2023), or due to enrollment challenges (such as for our ongoing clinical trial of pociredir in light of the more stringent inclusion and exclusion criteria); or
- there are any third-party challenges to our intellectual property or we need to defend against any intellectual property-related claim.

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our pipeline of product candidates or even continue our operations. A decline in the value of our company could also cause our stockholders to lose all or part of their investment.

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

We expect to devote substantial financial resources to our ongoing and planned activities, particularly as we continue our clinical development of pociredir, continue research and development and initiate additional clinical trials of, and seek regulatory approval for, this and any other product candidates. We expect our expenses to increase substantially in connection with our ongoing activities, particularly as we advance our preclinical activities and Phase 1b clinical trial of pociredir in SCD. In addition, if we obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, sales, marketing and distribution, particularly if we do not out-license our product candidate. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. Given current uncertainty in the capital markets and other factors, such funding may not be available on terms favorable to us or at all. If we are unable to raise capital when needed or on acceptable terms, we could be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

Our future capital requirements will depend on many factors, including:

- the progress, costs and results of our ongoing Phase 1b clinical trial of pociredir in SCD;
- additional planned clinical trials;
- the scope, progress, costs and results of discovery research, preclinical development, laboratory testing and clinical trials for any of our product candidates in additional indications or for any future product candidates that we may pursue;
- the number of and development requirements for other product candidates that we pursue;
- the costs, timing and outcome of regulatory review of our product candidates;
- our ability to enter into contract manufacturing arrangements for supply of API and manufacture of our product candidates and the terms of such arrangements;
- the success of our collaboration with MyoKardia or under our license agreement with CAMP4;
- our ability to establish and maintain additional strategic collaborations, licensing or other arrangements and the financial terms of such arrangements;
- the payment or receipt of milestones, royalties and other collaboration-based revenues, if any;
- the costs and timing of future commercialization activities, including product manufacturing, sales, marketing and distribution, for any of our product candidates for which we may receive marketing approval and that we do not out-license for commercialization;

•the amount and timing of revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval;

•the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property and proprietary rights and defending any intellectual property-related claims; and

•the extent to which we acquire or in-license other products, product candidates, technologies or data referencing rights.

As of December 31, 2024, we had cash, cash equivalents, and marketable securities of approximately $241.0 million. We believe that our cash, cash equivalents, and marketable securities as of December 31, 2024 will enable us to fund our operating expenses and capital expenditure requirements into at least 2027. However, we have based this estimate on assumptions that may prove to be wrong, and our operating plan may change as a result of many factors currently unknown to us. As a result, we could deplete our capital resources sooner than we currently expect.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain regulatory approval and achieve product sales. For example, we invested significant time and effort into developing losmapimod for FSHD but did not demonstrate a statistically significant difference between losmapimod and placebo on the primary endpoint in the Phase 3 REACH trial, for which we announced topline data in September 2024 and thereafter discontinued development. In addition, our product candidates, if approved, may not achieve commercial success. Commercial revenues, if any, will not be derived unless and until we can achieve sales of products, which we do not anticipate for several years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all, and may become even more difficult to obtain due to rising interest rates and the recent downturn in the U.S. capital markets and the biotechnology sector in general. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans. If adequate funds are not available to us on a timely basis, we may be required to delay, limit, reduce or terminate preclinical studies, clinical trials or other development activities for one or more of our product candidates or discovery stage programs or delay, limit, reduce or terminate our establishment of sales and marketing capabilities or other activities that may be necessary to bring our product candidates to market. We may also choose to further realign our operations to achieve additional operational efficiencies beyond the recent strategic realignment effected in September 2024.

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

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. We do not have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, our stockholders' ownership interests will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect our stockholders' rights as common stockholders. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, selling or licensing our assets, making capital expenditures or declaring dividends.

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

We have in the past relied, and in the future anticipate we will rely, in part on sales of our common stock through an at-the-market, or ATM, offering program. Increased volatility and decreases in market prices of equity securities generally and of our common stock in particular may have an adverse impact on our willingness and/or ability to continue to sell our common stock through our ATM offering program. Decreases in these sales could affect the cost or availability of equity capital, which could in turn have an adverse effect on our business, including current operations, future growth, revenues, net income and the market prices of our common stock.

In February 2024, we established a new ATM offering program to sell shares of our common stock having an aggregate offering price of up to $100.0 million from time to time. Given the overall volatility in the capital markets, we may not be willing or able to continue to raise equity capital through our ATM offering program. We may, therefore, need to turn to other sources of funding that may have terms that are not favorable to us, or reduce our business operations given capital constraints.

Alternative financing arrangements could involve issuances of one or more types of securities, including common stock, preferred stock, convertible debt, warrants to acquire common stock or other securities. These securities could be issued at or below the then prevailing market price for our common stock. In addition, if we issue debt securities, the holders of the debt would have a claim to our assets that would be superior to the rights of stockholders until the principal, accrued and unpaid interest and any premium or make-whole has been paid. In addition, if we borrow funds and/or issue debt securities through a subsidiary, the lenders and/or holders of those debt securities would have a right to payment that would be effectively senior to our equity ownership in the subsidiary, which would adversely affect the rights of holders of both our equity securities and, if any, our debt and debt securities.

Interest on any newly-issued debt securities and/or newly-incurred borrowings would increase our operating costs and reduce our net income, and these impacts may be material. If the issuance of new securities results in diminished rights to holders of our common stock, the market price of our common stock could be materially and adversely affected. Should the financing we require to sustain our working capital needs be unavailable or prohibitively expensive when we require it, the consequences could result in a material adverse effect on our business, operating results, financial condition and prospects.

Our operations have been focused on research and development and conducting clinical trials, which may make it difficult for stockholders to evaluate the success of our business to date and to assess our future viability.

We commenced activities in 2015 and are a clinical-stage biotechnology company. Our operations to date have been limited to organizing and staffing our company, business planning, raising capital, establishing our intellectual property, building our discovery platform, identifying drug targets and potential product candidates, in-licensing assets, producing drug substance and drug product material for use in clinical trials and conducting preclinical studies and clinical trials. We have not yet demonstrated our ability to successfully develop any product candidate, obtain regulatory approvals, manufacture a commercial scale product or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization or arrange for a third party to do so on our behalf. Consequently, any predictions stockholders make about our future success or viability may not be as accurate as they could be if we had a history of successfully developing and commercializing products.

In addition, as our business evolves, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors, such as our announcement in September 2024 that our Phase 3 REACH trial evaluating losmapimod for FSHD did not achieve its primary endpoint of change from baseline in relative surface area compared to placebo, and subsequent implementation of a plan to reprioritize research and development activities to focus on our other programs and reduction in workforce. If we are successful in moving our current pipeline programs through the clinic, we will need to transition at some point from a company with a research and development focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

We expect our financial condition and operating results to fluctuate significantly from quarter-to-quarter and year-to-year due to a variety of factors, many of which are beyond our control. Accordingly, stockholders should not rely upon the results of any quarterly or annual periods as indications of future operating performance.

Changes in tax laws or in their implementation or interpretation may adversely affect our business and financial condition.

The rules dealing with U.S. federal, state, and local income taxation are constantly under review by persons involved in the legislative process and by the Internal Revenue Service and the U.S. Treasury Department. Changes to tax laws (which changes may have retroactive application), including with respect to net operating losses and research and development tax credits, could adversely affect us or holders of our common stock. In recent years, many such changes have been made and changes are likely to continue to occur in the future. For example, under Section 174 of the U.S. Internal Revenue Code of

1986, as amended, or the Code, in taxable years beginning after December 31, 2021, expenses that are incurred for research and development in the United States will be capitalized and amortized, which may have an adverse effect on our cash flow. Future changes in tax laws could have a material adverse effect on our business, cash flow, financial condition or results of operations. We urge investors to consult with their legal and tax advisers regarding the implications of potential changes in tax laws on an investment in our common stock.

Our ability to use our net operating losses and research and development tax credit carryforwards to offset future taxable income may be subject to certain limitations.

As of December 31, 2024, we had federal net operating loss carryforwards of $5.0 million, which may be available to offset future taxable income and do not expire, but are limited in their usage to an annual deduction equal to 80% of annual taxable income. As of December 31, 2024, we had state net operating loss carryforwards of $6.2 million, which begin to expire in 2044. As of December 31, 2024, we also had federal orphan drug credits of $2.2 million, which begin to expire in 2044. As of December 31, 2024, we also had federal and state research and development tax credit carryforwards of $2.5 million and $0.2 million, respectively, which begin to expire in 2039. These net operating loss and tax credit carryforwards could expire unused and be unavailable to offset future income tax liabilities.

In general, under Section 382 of the Code, and corresponding provisions of state law, a corporation that undergoes an "ownership change," which is generally defined as a greater than 50% change, by value, in its equity ownership by certain stockholders over a three-year period, is subject to limitations on its ability to utilize its pre-change net operating losses and research and development tax credit carryforwards to offset future taxable income. We conducted an analysis under Section 382 of the Code to determine if historical changes in ownership would limit or otherwise restrict our ability to utilize our pre-change net operating losses and research and development tax credit carryforwards to offset future taxable income, and we determined that all net operating loss carryforwards and credits generated before September 12, 2024 are limited. As a result, the carryfowards before the ownership change date of September 12, 2024 are not available for utilization and have been written off. The carryfowards as of December 31, 2024 were generated after the ownership change on September 12, 2024. If we experience a change of control, as defined by Section 382, subsequent to December 31, 2024, utilization of the net operating loss carryforwards or research and development tax credit carryforwards would be subject to an annual limitation under Section 382.

We have a history of cumulative losses and anticipate that we will continue to incur significant losses in the foreseeable future; thus, we do not know whether or when we will generate taxable income necessary to utilize our net operating losses or research and development tax credit carryforwards.

Adverse developments affecting the financial services industry, such as actual events or concerns involving liquidity, defaults or non-performance by financial institutions or transactional counterparties, could adversely affect our current and projected business operations and financial condition and results of operations.

Events involving limited liquidity, defaults, non-performance or other adverse developments that affect financial institutions, transactional counterparties or other companies in the financial services industry or the financial services industry generally, or concerns or rumors about any events of these kinds or other similar risks, have in the past and may in the future lead to market-wide liquidity problems. In March 2023, a number of banks (e.g., Silicon Valley Bank, Signature Bank and Silvergate Capital Corp.) were placed into receivership, followed by First Republic Bank in May 2023. Although the Federal Deposit Insurance Corporation, or FDIC, and others have taken steps to reduce risk to uninsured depositors, borrowers under credit agreements, letters of credit and certain other financial instruments with such banks or any other financial institution that is placed into receivership by the FDIC may be unable to access undrawn amounts thereunder. Even though we assess our banking relationships as we believe necessary or appropriate, our access to funding sources and other credit arrangements in amounts adequate to finance or capitalize our current and projected future business operations could be significantly impaired by factors affecting the financial services industry or economy in general, such as these recent bank failures. These factors could also include, among others, liquidity constraints or failures, the ability to perform obligations under various types of financial, credit or liquidity agreements or arrangements, disruptions or instability in the financial services industry or financial markets, or concerns or negative expectations about the prospects for companies in the financial services industry and the supervision thereof. In addition, investor concerns regarding the United States or international financial systems could result in less favorable commercial financing terms, including higher interest rates or costs and tighter financial and operating covenants, or systemic limitations on access to credit and liquidity sources, thereby making it more difficult for us to acquire financing on acceptable terms or at all. Any decline in available funding or access to our cash and liquidity resources could, among other risks, adversely impact our ability to meet our operating expenses, financial obligations or fulfill our other obligations, result in breaches of our contractual obligations or result in violations of federal or state wage and hour laws, which could have material adverse effect on our liquidity and on our business, financial condition or results of operations.

Risks Related to the Discovery and Development of our Product Candidates

We are early in our development efforts and we currently have one product candidate in active clinical development. If we are unable to commercialize directly or out-license to a third party any of our product candidates or experience significant delays in doing so, our business will be materially harmed.

We are early in our development efforts, and we have advanced only two product candidates into clinical trials. In September 2024, we announced that REACH, our Phase 3 clinical trial of losmapimod for the treatment of FSHD, did not meet its primary endpoint and we suspended development of losmapimod. As a result, we currently only have one product candidate in active clinical development, pociredir for the treatment of SCD. We have invested substantially all of our efforts and financial resources in identifying and validating and conducting clinical trials on cellular drug targets that can potentially modulate gene expression to address the root cause of genetically-defined rare diseases. Our ability to generate product revenues, which we do not expect will occur for several years, if ever, will depend heavily on the successful development, regulatory approval and eventual commercialization of any of our product candidates. The success of any of our product candidates will depend on several factors, including the following:

- successfully completing preclinical studies and clinical trials;
- allowance by the FDA or other regulatory agencies of the INDs, clinical trial applications, or CTAs, or other regulatory filings;
- expanding and maintaining a workforce of experienced scientists and others to continue development efforts;
- applying for and receiving marketing approvals from applicable regulatory authorities;
- obtaining and maintaining intellectual property protection and regulatory exclusivity;
- making arrangements with third-party manufacturers for, or establishing, commercial manufacturing capabilities;
- establishing sales, marketing and distribution capabilities and successfully launching commercial sales, if and when approved, whether alone or in collaboration with others;
- acceptance, if and when approved, by patients, the medical community and third-party payors;
- effectively competing with other therapies;
- obtaining and maintaining coverage, adequate pricing and adequate reimbursement from third-party payors, including government payors;
- maintaining, enforcing, defending and protecting our rights in our intellectual property portfolio;
- not infringing, misappropriating or otherwise violating others' intellectual property or proprietary rights; and
- maintaining a continued acceptable safety profile following receipt of any regulatory approvals.

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

We may not be successful in our efforts to build a pipeline of product candidates.

Our current strategy is focused on developing small molecules to improve the lives of patients with genetically defined rare diseases. Even if we are successful in identifying drug targets and potential product candidates, such candidates that we identify may not be suitable for clinical development, including as a result of being shown to have harmful side effects or other characteristics that indicate that they are unlikely to receive marketing approval and achieve market acceptance. Identifying, developing, obtaining regulatory approval for and commercializing additional product candidates will require substantial additional funding and is prone to the risks of failure inherent in product development. We cannot provide stockholders any assurance that we will be able to successfully identify additional product candidates, advance any additional product candidates through the development process or successfully commercialize any such additional product candidates. Regulatory authorities have substantial discretion in the approval process and may cause delays in the approval or rejection of an application. As a result of these factors, it is difficult for us to predict the time and cost of product candidate development. There can be no assurance that any development problems we experience in the future related to our discovery technologies or any of our research or development programs will not cause significant delays or unanticipated costs, or that such development problems can be solved. If we do not successfully identify, develop, obtain regulatory approval for and commercialize product candidates, we will not be able to generate product revenues.

Clinical drug development involves a lengthy and expensive process, with an uncertain outcome. The results of preclinical studies and early clinical trials may not be predictive of future results. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

We currently only have one product candidate in active clinical development following our recent decision to suspend further development of losmapimod. The risk of failure for product candidates is high and it is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive regulatory approval. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidate in humans. We have not yet completed a pivotal clinical trial of any product candidate that demonstrated that our product candidate is safe and effective for its intended use. For example, in September 2024, we announced that REACH, our Phase 3 trial evaluating losmapimod in patients with FSHD, did not successfully achieve its primary endpoint as compared to placebo, and we suspended further development of losmapimod. Additionally, pociredir, our clinical-stage candidate to treat SCD, is an embryonic ectoderm development, or EED, inhibitor. EED is a member of the PRC2 complex, which also includes EZH2. There are approved products in the EZH2 class of medications and their approved labeling outlines safety risks, including an increased risk of malignancies. In the event that pociredir has similar safety risks as other PRC2 medications, this could impact its acceptance. Even if the clinical trials are successful, changes in marketing approval policies during the development period, changes in or the enactment or promulgation of additional statutes, regulations or guidance or changes in regulatory review for each submitted product application may cause delays in the approval or rejection of an application.

Before we can commence clinical trials for a product candidate, we must complete extensive preclinical testing and studies that support our planned INDs and other regulatory filings in the United States and abroad. We cannot be certain of the timely completion or outcome of our preclinical testing and studies and cannot predict if the FDA or other regulatory agencies will accept our proposed clinical programs or if the outcome of our preclinical testing and studies will ultimately support the further development of our current or future product candidates. As a result, we cannot be sure that we will be able to submit INDs or similar applications for our preclinical programs on the timelines we expect, if at all, and we cannot be sure that submission of INDs or similar applications will result in the FDA or other regulatory authorities allowing clinical trials to begin or continue. For example, in February 2023, the FDA imposed a clinical hold on our IND for pociredir in SCD. We worked diligently to resolve the hold as soon as possible, and in August 2023, the FDA lifted the clinical hold. Product candidates are subject to continued preclinical safety studies, which may be conducted concurrent with our clinical testing. The outcomes of these safety studies may delay the launch of or enrollment in future clinical trials and could impact our ability to continue to conduct our clinical trials.

Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, or at all. For example, we revised the inclusion and exclusion criteria of our clinical trial of pociredir in SCD to address the clinical hold imposed by the FDA, and are experiencing some difficulty enrolling patients who meet the updated more stringent criteria. While we are expanding our clinical trial sites, including outside the United States, to identify suitable patients that meet the new criteria, there can be no certainty as to whether we will be successful in completing the clinical trial with its revised design. A failure of one or more clinical trials can occur at any stage of testing, which may result from a multitude of factors, including, but not limited to, flaws in study design, dose selection issues, placebo effects, patient enrollment criteria and failure to demonstrate favorable safety or efficacy traits. In September 2024 we suspended further development of losmapimod after topline data from the Phase 3 REACH trial indicated that it did not achieve its primary endpoint of change from baseline in relative surface area, a measure of reachable work space, compared to placebo. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and preliminary or interim results of a clinical trial do not necessarily predict final results. For example, our product candidates may fail to show the desired safety and efficacy in clinical development despite positive results in preclinical studies or having successfully advanced through initial clinical trials. A lack of clinical benefit may be due to insufficient dosing or for other reasons. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in preclinical testing and earlier-stage clinical trials, 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. Furthermore, the failure of any of our product candidates to demonstrate safety and efficacy in any clinical trial could negatively impact the perception of our other product candidates and/or cause the FDA or other regulatory authorities to require additional testing before approving any of our product candidates.

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

- regulators or institutional review boards, or IRBs, may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching, or fail to reach, agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- regulators may decide the design of our clinical trials is flawed, for example if our trial protocol does not evaluate treatment effects in trial subjects for a sufficient length of time;
- clinical trials of our product candidates may produce negative or inconclusive results, such as with the recent Phase 3 REACH trial, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- we may be unable to establish clinical endpoints that applicable regulatory authorities would consider clinically meaningful, or, if we seek accelerated approval, biomarker efficacy endpoints that applicable regulatory authorities would consider likely to predict clinical benefit;
- preclinical testing may produce results based on which we may decide, or regulators may require us, to conduct additional preclinical studies before we proceed with certain clinical trials, limit the scope of our clinical trials, halt ongoing clinical trial(s) or abandon product development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate (for example, we initially experienced difficulty enrolling patients who met the updated inclusion and exclusion criteria for our trial of pociredir in SCD) or participants may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- we may decide, or regulators or IRBs may require us, to suspend or terminate clinical trials of our product candidates for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;
- regulators or IRBs may require us to perform additional or unanticipated clinical trials to obtain approval or we may be subject to additional post-marketing testing requirements to maintain regulatory approval;
- regulators may revise the requirements for approving our product candidates, or such requirements may not be as we anticipate;
- the cost of clinical trials of our product candidates may be greater than we anticipate;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate;
- our product candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators or IRBs to suspend or terminate the trials;
- unforeseen global instability, including political instability, such as the Russian invasion of Ukraine or hostilities in Israel, Lebanon and the Gaza Strip, changes in U.S. economic policy that adversely impact the U.S. economy and/or economies worldwide, or instability from an outbreak of pandemic or contagious disease in or around the countries in which we conduct our clinical trials (such as closure of clinical trial sites, like we experienced in our ReDUX4 clinical trial due to COVID-19), could delay the commencement or rate of completion of our clinical trials; and
- regulators may withdraw their approval of a product or impose restrictions on its distribution, such as in the form of a risk evaluation and mitigation strategy, or REMS.

Further, in February 2023, the FDA imposed a clinical hold on our IND for pociredir in SCD, which halted our clinical trial until the FDA lifted the clinical hold in August 2023.

If we are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we are unable to successfully complete clinical trials of our product candidates or other testing, if the results of these trials or tests are not positive, such as our recent topline data from the Phase 3 REACH trial, or are only modestly positive or if there are safety concerns, we may:

- suspend further development (such as with losmapimod for FSHD);
- be delayed in obtaining marketing approval for our product candidates;
- not obtain marketing approval at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling or a REMS that includes significant use or distribution restrictions or safety warnings;
- be subject to additional post-marketing testing requirements; or
- have the product removed from the market after obtaining marketing approval.

Our product development costs will also increase if we experience delays in testing or in obtaining marketing approvals. We do not know whether any of our preclinical studies or clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. We may also determine to change the design or protocol of one or more of our clinical trials, including to add additional patients or arms, which could result in increased costs and expenses and/or delays. Significant preclinical study or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

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

Identifying and qualifying patients to participate in and complete clinical trials for our product candidates is critical to our success. Successful and timely completion of clinical trials requires that we enroll a sufficient number of patients that meet both the enrollment criteria, and who remain in the trial until its conclusion. For example, in our Phase 1b trial of pociredir, although we enrolled six subjects in the initial cohort, only three subjects remained evaluable as of the initial data cutoff date. Subsequently, we modified the study protocol to monitor subject adherence. However, if such protocols do not improve adherence and improve compliance, we may not be able to generate meaningful data. Furthermore, we may not be able to initiate or continue clinical trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or similar regulatory authorities outside of the United States. We revised the design of our clinical trial of pociredir in SCD to address the clinical hold imposed by the FDA, and there can be no certainty as to whether we will be successful in completing the clinical trial with its revised design, which include updated inclusion and exclusion criteria and thus a narrower set of eligible patients, which is making enrollment difficult despite opening a number of sites for such trial. Because of our primary focus on genetically-defined rare diseases, we may have difficulty enrolling a sufficient number of eligible patients.

Patient enrollment is affected by a variety of other factors, including:

- the prevalence and severity of the disease under investigation;
- the eligibility criteria for the trial in question (such as with our trial of pociredir for SCD);
- the perceived risks and benefits of the product candidate under trial;
- the requirements of the trial protocols, including invasive procedures;
- the availability of existing treatments for the indications for which we are conducting clinical trials;
- the ability to recruit clinical trial investigators with the appropriate competencies and experience;
- the efforts to facilitate timely enrollment in clinical trials;
- the patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment;

•the proximity and availability of clinical trial sites for prospective patients;

•the conduct of clinical trials by competitors for product candidates that treat the same indications as our current or future product candidates;

•the ability to identify specific patient populations for biomarker-defined trial cohort(s); and

•the cost to, or lack of adequate compensation for, prospective patients.

Our inability to locate and enroll a sufficient number of patients for our clinical trials would result in significant delays, could require us to abandon one or more clinical trials altogether and could delay or prevent our receipt of necessary regulatory approvals.

Enrollment delays in our clinical trials may result in increased development costs for our product candidates, which would cause the value of our company to decline and limit our ability to obtain additional financing.

If serious adverse events or unacceptable side effects are identified during the development of our product candidates, we may need to abandon or limit our development of our product candidate.

If our product candidates are associated with serious adverse events or undesirable side effects in clinical trials or have characteristics that are unexpected in clinical trials or preclinical testing, we may need to abandon their development or limit development to more narrow uses or subpopulations in which the serious adverse events, undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective.

For example, in February 2023, the FDA placed our IND for pociredir on clinical hold based on hematological malignancies observed in nonclinical toxicology studies. We addressed the FDA's concern as diligently as possible, including FDA's request for information about an SCD patient population with an appropriate benefit-risk profile for further clinical development of pociredir, and FDA's request for information to define the potential risk in any further studies that may be conducted in healthy volunteers. Although the FDA lifted the clinical hold in August 2023, we cannot make assurances that patients treated with pociredir will not develop hematological malignancies or other adverse events in the future. We also cannot make assurances that additional observations in preclinical studies of hematological malignancies or other adverse events will not occur. If such additional adverse events were to emerge, further advancement of our clinical studies could be halted or delayed and we may not receive regulatory approval for pociredir. Even if we receive regulatory approval for pociredir, our labeling may be restricted and/or market acceptance for our product may be diminished, and the commercial potential of our pociredir program may be materially and negatively impacted.

In pharmaceutical development, many compounds that initially show promise in early-stage or clinical testing are later found to cause side effects that delay or prevent further development of the compound.

Additionally, if results of our clinical trials reveal unacceptable side effects, we, the FDA or the IRBs at the institutions in which our studies are conducted could suspend or terminate our clinical trials or the FDA or comparable foreign regulatory authorities could order us to cease clinical trials or deny approval of our product candidates for any or all targeted indications. Treatment-related side effects could also affect patient recruitment or the ability of enrolled patients to complete any of our clinical trials. If we elect or are forced to suspend or terminate any clinical trial of our product candidates, the commercial prospects of such product candidate will be harmed, and our ability to generate product revenue from such product candidate will be delayed or eliminated. Any of these occurrences could materially harm our business.

If any of our product candidates receives marketing approval and we, or others, later discover that the drug is less effective than previously believed or causes undesirable side effects that were not previously identified, our ability to market the drug could be compromised.

Clinical trials of our product candidates are conducted in carefully defined subsets of patients who have agreed to enter into clinical trials. Consequently, it is possible that our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any, or alternatively fail to identify undesirable side effects. If one or more of our product candidates receives regulatory approval, and we, or others, later discover that they are less effective than previously believed, or cause undesirable side effects, a number of potentially significant negative consequences could result, including:

•withdrawal or limitation by regulatory authorities of approvals of such product;

•seizure of the product by regulatory authorities;

•recall of the product;

•restrictions on the marketing of the product or the manufacturing process for any component thereof;

•requirement by regulatory authorities of additional warnings on the label, such as a "black box" warning or contraindication;

•requirement that we implement a REMS or create a medication guide outlining the risks of such side effects for distribution to patients;

•commitment to expensive post-marketing studies as a prerequisite of approval by regulatory authorities of such product;

•the product may become less competitive;

•initiation of regulatory investigations and government enforcement actions;

•initiation of legal action against us to hold us liable for harm caused to patients; and

•harm to our reputation and resulting harm to physician or patient acceptance of our products.

Any of these events could prevent us from achieving or maintaining market acceptance of a particular product candidate, if approved, and could significantly harm our business, financial condition, and results of operations.

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

Because we have limited financial and managerial resources, we are focusing our research and development efforts on rare neuromuscular, muscular, hematologic and central nervous system disorders. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. For example, we recently suspended further development of losmapimod after devoting significant time, effort and capital on the program but it did not meet its primary endpoint in the Phase 3 REACH trial. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. Failure to allocate resources or capitalize on strategies in a successful manner will have an adverse impact on our business.

We are conducting a clinical trial of pociredir in patients with SCD in Africa, and the FDA may not accept data from trials conducted in such locations.

We are currently conducting a Phase 1b clinical trial of pociredir in patients with SCD in Africa. We may also conduct additional clinical trials of other product candidates outside the United States. Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of these data is subject to conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and be performed by qualified investigators in accordance with ethical principles. The trial population must also adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will depend on its determination that the trials also complied with all applicable U.S. laws and regulations, including good clinical practices, and FDA's ability to validate the data. If the FDA does not accept the data from any trial that we conduct outside the United States, it would likely result in the need for additional trials, which would be costly and time-consuming and could delay or permanently halt our development of the applicable product candidates.

Risks Related to the Commercialization of our Product Candidates

Even if any of our product candidates receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success, and the market opportunity for any of our product candidates, if approved, may be smaller than we estimate.

If any of our product candidates receives marketing approval, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. Efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may not be successful. If our product candidates do not achieve an adequate level of acceptance, we may not generate significant product revenues and we may not become profitable. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy and potential advantages of our product candidates compared to the advantages and relative risks of alternative treatments;
- the effectiveness of sales and marketing efforts;
- the cost of treatment in relation to alternative treatments, including any similar generic treatments;
- our ability to offer our products, if approved, for sale at competitive prices;
- the clinical indications for which the product is approved;
- the convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support;
- the timing of market introduction of competitive products;
- the availability of third-party coverage and adequate reimbursement, and patients' willingness to pay out of pocket for required co-payments or in the absence of third-party coverage or adequate reimbursement;
- the prevalence and severity of any side effects; and
- any restrictions on the use of our products, if approved, together with other medications.

Our assessment of the potential market opportunity for our product candidates is based on industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties, one of which we commissioned. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. While we believe these industry publications and third-party research, surveys and studies are reliable, we have not independently verified such data. Our estimates of the potential market opportunities for our product candidates include several key assumptions based on our industry knowledge, industry publications and third-party research, surveys and studies, which may be based on a small sample size and fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, no independent source has verified such assumptions. If any of our assumptions or estimates, or these publications, research, surveys or studies prove to be inaccurate, then the actual market for our product candidate may be smaller than we expect, and as a result our product revenue may be limited and it may be more difficult for us to achieve or maintain profitability.

If we are unable to establish sales, marketing and distribution capabilities or enter into sales, marketing and distribution agreements with third parties, we may not be successful in commercializing our product candidates if and when they are approved.

We do not have a sales or marketing infrastructure and have no experience in the sale, marketing or distribution of pharmaceutical products. To achieve commercial success for any product for which we have obtained marketing approval, we will need to establish a sales, marketing and distribution organization, either ourselves or through collaborations or other arrangements with third parties.

In the future, we may build a focused, specialty sales and marketing infrastructure to market one or more of our product candidates in the United States, if and when they are approved. There are risks involved with establishing our own sales, marketing and distribution capabilities. For example, recruiting and training a sales force is expensive and time-consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. These efforts may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to commercialize our products on our own include:

- our inability to recruit, train and retain adequate numbers of effective sales, marketing, coverage or reimbursement, customer service, medical affairs and other support personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future products;
- the inability of reimbursement professionals to negotiate arrangements for formulary access, reimbursement and other acceptance by payors;
- the inability to price our products at a sufficient price point to ensure an adequate and attractive level of profitability;
- restricted or closed distribution channels that make it difficult to distribute our products to segments of the patient population;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we are unable to establish our own sales, marketing and distribution capabilities and we enter into arrangements with third parties to perform these services, our product revenues and our profitability, if any, are likely to be lower than if we were to market, sell and distribute any products that we develop ourselves. 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. Further, there can be no guarantee that we will be able to successfully enter into arrangements with third parties to perform sales, marketing or distribution services. If we do not establish sales, marketing and distribution capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

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

The development and commercialization of new drug products is highly competitive. We face competition with respect to our current product candidates, and will face competition with respect to any product candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of many of the disease indications for which we are developing our product candidates. Some of these competitive products and therapies are based on scientific approaches that are the same as or similar to our approach, and others are based on entirely different approaches. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

For example, we are aware of several product candidates in clinical development that could be competitive with product candidates that we may successfully develop and commercialize. See Item 1 “Business — Competition” for more information.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. For example, in December 2023, the FDA approved CASGEVY (exagamglogene autotemcel) and LYFGENIA (lovotibeglogene autotemcel), the first ex vivo cell-based gene therapies for the treatment of SCD. CASGEVY has also been FDA-approved for the treatment of transfusion-dependent beta-thalassemia. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic products. If our product candidates achieve marketing approval, we expect that they will be priced at a significant premium over competitive generic products.

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do.

Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

If the market opportunities for our product candidates are smaller than we believe they are, our revenue may be adversely affected, and our business may suffer. Because certain of the target patient populations of our product candidates are small, and the addressable patient population even smaller, we must be able to successfully identify patients and capture a significant market share to achieve profitability and growth.

We primarily focus our research and product development on treatments for genetically-defined rare diseases. Given the small number of patients who have the rare diseases that we are targeting, it is critical to our ability to grow and become profitable that we continue to successfully identify patients with these rare diseases. Our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on our beliefs and estimates. These estimates have been derived from a variety of sources, including the scientific literature, surveys of clinics, patient foundations or market research that we conducted, and may prove to be incorrect or contain errors. New studies may change the estimated incidence or prevalence of these diseases. The number of patients may turn out to be lower than expected. The effort to identify patients with diseases we seek to treat is in early stages, and we cannot accurately predict the number of patients for whom treatment might be possible. Additionally, the potentially addressable patient population for each of our product candidates may be limited or may not be amenable to treatment with our product candidates, and new patients may become increasingly difficult to identify or gain access to, which would adversely affect our results of operations and our business. Further, even if we obtain significant market share for our product candidates, because the potential target populations for many of the indications we are evaluating are very small, we may never achieve profitability despite obtaining such significant market share.

Further, the pricing and reimbursement of our product candidates, if approved, is uncertain, but must be adequate to support commercial infrastructure. If we are unable to obtain adequate levels of reimbursement, our ability to successfully market and sell any approved products will be adversely affected.

We rely, and expect to continue to rely, on CMOs to manufacture our product candidates. If we are unable to enter into such arrangements as expected or if such organizations do not meet our supply requirements, development and/or commercialization of our product candidates may be delayed.

We do not have any manufacturing facilities and rely, and expect to continue to rely, on third parties to manufacture clinical supplies of our product candidates and we expect to rely on third parties to manufacture commercial supplies of our products, if and when approved for marketing by applicable regulatory authorities, as well as for packaging, sterilization, storage, distribution and other production logistics. If we are unable to enter into such arrangements on the terms or timeline we expect, development and/or commercialization of our product candidates may be delayed.

If these third parties do not successfully carry out their contractual duties, meet expected deadlines or manufacture our product candidates in accordance with regulatory requirements, if there are disagreements between us and such parties or if such parties are unable to expand capacities to support commercialization of any of our product candidates for which we obtain marketing approval, we may not be able to fulfill, or may be delayed in producing sufficient product candidates to meet, our supply requirements, or we may be forced to manufacture the materials ourselves, for which we may not have the capabilities or resources, or enter into an agreement with a different manufacturer, which we may not be able to do on

reasonable terms, if at all. In either scenario, our clinical trial supply could be delayed significantly as we establish alternative supply sources. In some cases, the technical skills required to manufacture our products or product candidates may be unique or proprietary to the original manufacturer and we may have difficulty, or there may be contractual restrictions prohibiting us from, transferring such skills to a back-up or alternate supplier, or we may be unable to transfer such skills at all.

In addition, if we are required to change manufacturers for any reason, we will be required to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations. We will also need to verify, such as through a manufacturing comparability study, that any new manufacturing process will produce our product candidate according to the specifications previously submitted to the FDA or another regulatory authority. The delays associated with the verification of a new manufacturer could negatively affect our ability to develop product candidates or commercialize our products in a timely manner or within budget. Furthermore, a manufacturer may possess technology related to the manufacture of our product candidate that such manufacturer owns independently. This would increase our reliance on such manufacturer or require us to obtain a license from such manufacturer in order to have another manufacturer manufacture our product candidates. In addition, changes in manufacturers often involve changes in manufacturing procedures and processes, which could require that we conduct bridging studies between our prior clinical supply used in our clinical trials and that of any new manufacturer. We may be unsuccessful in demonstrating the comparability of clinical supplies which could require the conduct of additional clinical trials. These facilities may also be affected by natural disasters, such as floods or fire, as well as public health issues (for example, an outbreak of a contagious disease such as COVID-19), or such facilities could face manufacturing issues, such as contamination or regulatory concerns following a regulatory inspection of such facility.

Our third-party manufacturers will be subject to inspection and approval by the FDA before we can commence the manufacture and sale of any of our product candidates, and thereafter subject to FDA inspection from time to time. Failure by our third-party manufacturers to pass such inspections and otherwise satisfactorily complete the FDA approval regimen with respect to our product candidates may result in regulatory actions such as the issuance of FDA Form 483 notices of observations, warning letters or injunctions or the loss of operating licenses.

We or our third-party manufacturers may also encounter shortages in the raw materials or API necessary to produce our product candidates in the quantities needed for our clinical trials or, if our product candidates are approved, in sufficient quantities for commercialization or to meet an increase in demand, as a result of capacity constraints or delays or disruptions in the market for the raw materials or API, including shortages caused by the purchase of such raw materials or API by our competitors or others. The failure of us or our third-party manufacturers to obtain the raw materials or API necessary to manufacture sufficient quantities of our product candidates, may have a material adverse effect on our business.

Our reliance on third parties increases the risk that we will not have sufficient quantities of our product candidate or products or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts.

We do not have any manufacturing facilities. Although we believe we have obtained sufficient quantities of pociredir from a CMO for the completion of our Phase 1b clinical trial for SCD, we cannot be sure we have correctly estimated our drug product requirements, which could delay, prevent or impair our development efforts.

We expect to rely on third parties for the manufacture of pociredir for any future clinical trials and for the manufacture of any future product candidates for preclinical and clinical testing. We also expect to rely on third-party manufacturers or third-party collaborators for the manufacture of commercial supply of any other product candidates for which we or our collaborators obtain marketing approval. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts.

In addition, legislative proposals are pending that, if enacted, could negatively impact U.S. funding for certain biotechnology providers having relationships with foreign adversaries or which pose a threat to national security. The potential downstream adverse impacts on entities having commercial relationships with any impacted biotechnology providers are unknown but may include supply chain disruptions or delays. Our product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us.

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply or a source for bulk drug substance. If any of our future contract manufacturers cannot perform as agreed, we may be required to replace such manufacturers. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur added costs and delays in identifying and qualifying any such replacement.

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

Even if we are able to commercialize any product candidates, the products may become subject to unfavorable pricing regulations, third-party coverage or reimbursement practices or healthcare reform initiatives, which could harm our business.

The regulations that govern marketing approvals, pricing, coverage and reimbursement for new drug products vary widely from country to country. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay our commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if our product candidates obtain marketing approval. See Item 1 "Business — Government Regulation and Product Approval — Pharmaceutical Insurance Coverage and Health Care Reform."

Our ability to commercialize any product candidates successfully also will depend in part on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. 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. Coverage and reimbursement may not be available for any product that we commercialize and, even if these are available, the level of reimbursement may not be satisfactory. Reimbursement may affect the demand for, or the price of, any product candidate for which we obtain marketing approval. Obtaining and maintaining adequate reimbursement for our products may be difficult. We may be required to conduct expensive pharmacoeconomic studies to justify coverage and reimbursement or the level of reimbursement relative to other therapies. If coverage and adequate reimbursement are not available or reimbursement is available only to limited levels, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval. Coverage and reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor's determination that use of a product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

There may be significant delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA or similar regulatory authorities outside of the United States. Moreover, eligibility for coverage and reimbursement does not imply that a drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution expenses. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Our inability to promptly obtain coverage and adequate reimbursement rates from both government-funded and private payors for any approved products that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

There can be no assurance that our product candidates, even if they are approved for sale in the United States or in other countries, will be considered medically reasonable and necessary for a specific indication or cost-effective by third-party payors, or that coverage and an adequate level of reimbursement will be available or that third-party payors' reimbursement policies will not adversely affect our ability to sell our product candidates profitably.

Our future growth depends, in part, on our ability to penetrate foreign markets, where we would be subject to additional regulatory burdens and other risks and uncertainties that, if they materialize, could harm our business.

Our future profitability will depend, in part, on our ability to commercialize our product candidates in markets outside of the United States and the European Union. If we commercialize our product candidates in foreign markets, we will be subject to additional risks and uncertainties, including:

- economic weakness, including inflation, or political instability in particular economies and markets, which could include localized disputes that have a broader regional or global impact (such as the Russian invasion of Ukraine or recent hostilities in Israel, Lebanon, and the Gaza Strip);
- the burden of complying with complex and changing foreign regulatory, tax, accounting and legal requirements, many of which vary between countries;
- different medical practices and customs in foreign countries affecting acceptance in the marketplace;
- tariffs and trade barriers, as well as other governmental controls and trade restrictions;
- other trade protection measures, import or export licensing requirements or other restrictive actions by U.S. or foreign governments (such as the recent announced tariffs by the current U.S. administration);
- longer accounts receivable collection times;
- longer lead times for shipping;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- workforce uncertainty in countries where labor unrest is common;
- language barriers for technical training;
- reduced protection of intellectual property rights in some foreign countries, and related prevalence of generic alternatives to therapeutics;
- foreign currency exchange rate fluctuations and currency controls;
- differing foreign reimbursement landscapes;
- uncertain and potentially inadequate reimbursement of our products; and
- the interpretation of contractual provisions governed by foreign laws in the event of a contract dispute.

If risks related to any of these uncertainties materializes, it could have a material adverse effect on our business.

Clinical trial and product liability lawsuits against us could divert our resources and could cause us to incur substantial liabilities and to limit commercialization of any products that we may develop.

We face an inherent risk of clinical trial and product liability exposure related to the testing of our product candidates in human clinical trials, and we will face an even greater risk if we commercially sell any products that we may develop. While we currently have no products that have been approved for commercial sale, the current and future use of product candidates by us in clinical trials, and the sale of any approved products in the future, may expose us to liability claims. These claims might be made by patients that use the product, healthcare providers, pharmaceutical companies or others selling such products. If we cannot successfully defend ourselves against claims that our product candidates or products caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidates or products that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend any related litigation;
- substantial monetary awards to trial participants or patients;
- loss of revenue;
- reduced resources of our management to pursue our business strategy; and
- the inability to commercialize any products that we may develop.

We currently hold $10 million in clinical trial liability insurance coverage in the aggregate, with a per incident limit of $10 million, which may not be adequate to cover all liabilities that we may incur. We may need to increase our insurance coverage as we expand our clinical trials or if we commence commercialization of our product candidates. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise. If a successful clinical trial or product liability claim or series of claims is brought against us for uninsured liabilities or in excess of insured liabilities, our assets may not be sufficient to cover such claims and our business operations could be impaired.

Risks Related to our Dependence on Third Parties

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

We currently rely on third-party contract CROs to conduct our clinical trials. We plan to rely on third-party CROs or third-party research collaboratives to conduct any future clinical trials. We do not plan to independently conduct clinical trials of our other product candidates. We expect to continue to rely on third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials. These agreements might terminate for a variety of reasons, including a failure to perform by the third parties. If we need to enter into alternative arrangements, our product development activities might be delayed.

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities.

If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully develop and commercialize our product candidates. Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors.

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

We have entered into, and may in the future enter into, collaborations with third parties for the discovery, development or commercialization of our product candidates. If our collaborations are not successful, we may not be able to capitalize on the market potential of these product candidates and our business could be adversely affected.

We have a collaboration and license agreement with MyoKardia (for certain genetically defined cardiomyopathies). We may in the future enter into additional development, distribution or marketing arrangements with third parties with respect to our other existing or future product candidates. Our likely collaborators for any such sales, marketing, distribution, development, licensing or broader collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. These third party arrangements generally do not provide us with the ability to control the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on our collaborators' abilities and efforts to successfully perform the functions assigned to them in these arrangements.

Collaborations that we enter into, including our collaboration with MyoKardia, may not be successful, and any success will depend heavily on the efforts and activities of such collaborators. Collaborations pose a number of risks, including the following:

- collaborators have significant discretion in determining the amount and timing of efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- collaborators may not pursue development of any of our product candidates or may elect not to continue or renew development programs based on results of clinical trials or other studies, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;

•collaborators may not pursue commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew commercialization programs based on results of clinical trials or other studies, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that may divert resources or create competing priorities;

•collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;

•we may not have access to, or may be restricted from disclosing, certain information regarding product candidates being developed or commercialized under a collaboration and, consequently, may have limited ability to inform our stockholders about the status of such product candidates on a discretionary basis;

•collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates and products if the collaborators believe that the competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;

•product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;

•a collaborator may fail to comply with applicable regulatory requirements regarding the development, manufacture, distribution or marketing of a product candidate or product;

•a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product or products;

•disagreements with collaborators, including disagreements over intellectual property or proprietary rights, contract interpretation or the preferred course of development, might cause delays or terminations of the research, development or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time-consuming and expensive;

•collaborators may not properly obtain, maintain, enforce, defend or protect our intellectual property or proprietary rights or may use our proprietary information in such a way as to potentially lead to disputes or legal proceedings that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;

•disputes may arise with respect to the ownership of intellectual property developed pursuant to our collaborations;

•collaborators may infringe, misappropriate or otherwise violate the intellectual property or proprietary rights of third parties, which may expose us to litigation and potential liability; and

•collaborations may be terminated for the convenience of the collaborator (e.g., our former collaboration with Acceleron Pharma, Inc.), and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner, or at all. If any collaborations that we enter into do not result in the successful development and commercialization of products or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development of our product candidates could be delayed and we may need additional resources to develop our product candidates. All of the risks relating to product development, regulatory approval and commercialization described herein also apply to the activities of our collaborators.

Additionally, subject to its contractual obligations to us, if a collaborator of ours is involved in a business combination, the collaborator might deemphasize or terminate the development or commercialization of any product candidate licensed to it by us. For example, in November 2020, subsequent to our entering into the MyoKardia collaboration agreement, MyoKardia was acquired by Bristol-Myers Squibb Company. Bristol-Myers Squibb Company could determine to reprioritize MyoKardia's development programs such that it ceases to diligently pursue the development of our programs and/or cause the agreement between MyoKardia and us to terminate. If our collaborator terminates its agreement with us, we may find it more difficult to attract new collaborators and our perception in the business and financial communities could be adversely affected.

If we are not able to establish or maintain collaborations, we may have to alter our development and commercialization plans and our business could be adversely affected.

For some of our product candidates, we may decide to collaborate with pharmaceutical or biotechnology companies for the development and potential commercialization of those product candidates. For example, we entered into a collaboration and license agreement with Sanofi, granting Sanofi an exclusive license under certain intellectual property rights to commercialize losmapimod outside of the United States (which Sanofi has terminated for convenience in light of the REACH trial results). In addition, in July 2020, we entered into a collaboration and license agreement with MyoKardia to identify and validate potential biological targets for the potential treatment of certain genetically defined cardiomyopathies. We face significant competition in seeking appropriate collaborators, and a number of more established companies may also be pursuing strategies to license or acquire third-party intellectual property rights that we consider attractive. These established companies may have a competitive advantage over us due to their size, financial 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. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge, and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for our product candidate.

We may also be restricted under existing or future license agreements from entering into agreements on certain terms with potential collaborators. Under our collaboration with MyoKardia, we are restricted from researching, developing, manufacturing, commercializing, using, or otherwise exploiting any compound or product (a) that is a compound or product under the agreement that is directed against certain targets identified by us in the performance of the research activities for the treatment, prophylaxis, or diagnosis of any indication or (b) for the treatment of any genetically defined cardiomyopathies shown to be related to certain specified genes of interest that are modulated by the targets chosen by MyoKardia under our collaboration, in each case, while we are performing the research activities pursuant to the research plan and for a specified period thereafter. Further, our agreement with Sanofi included certain restrictions on our ability to research, develop, manufacture, commercialize, use, or otherwise exploit any compound or product that binds or otherwise modulates p38a/b MAPK anywhere in the world, except losmapimod in the United States.

Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical and biotechnology companies that have resulted in a reduced number of potential future collaborators.

If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms or at all, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market.

Risks Related to our Intellectual Property

If we are unable to obtain, maintain, enforce and protect patent protection for our technology and product candidates or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully develop and commercialize our technology and product candidates may be adversely affected.

Our success depends in large part on our ability to obtain and maintain protection of the intellectual property we may own solely and jointly with others or may license from others, particularly patents, in the United States and other countries with respect to any proprietary technology and product candidates we develop. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our product candidates that are important to our business and by in-licensing intellectual property related to our technologies and product candidates. If we are unable to obtain or maintain patent protection with respect to any proprietary technology or product candidate, our business, financial condition, results of operations and prospects could be materially harmed.

The patent prosecution process is expensive, time-consuming and complex, and we may not be able to file, prosecute, maintain, defend or license all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Moreover, in some circumstances, we do not have the right to control the preparation, filing and prosecution of patent applications, or to maintain, enforce and defend the patents, covering technology that we license from third parties. Therefore, these in-licensed patents and applications may not be prepared, filed, prosecuted, maintained, defended and enforced in a manner consistent with the best interests of our business.

The patent position of pharmaceutical and biotechnology companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. In addition, the scope of patent protection outside of the United States is uncertain and laws of foreign countries may not protect our rights to the same extent as the laws of the United States or vice versa. For example, European patent law restricts the patentability of methods of treatment of the human body more than United States law does. With respect to both owned and in-licensed patent rights, we cannot predict whether the patent applications we and our licensors are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient protection from competitors. Further, we may not be aware of all third-party intellectual property rights potentially relating to our product candidates. In addition, publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not published at all. Therefore, neither we nor our licensors can know with certainty whether either we or our licensors were the first to make the inventions claimed in the patents and patent applications we own or in-license now or in the future, or that either we or our licensors were the first to file for patent protection of such inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our owned and in-licensed patent rights are highly uncertain. Moreover, our owned and in-licensed pending and future patent applications may not result in patents being issued which protect our technology and product candidates, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents and our ability to obtain, protect, maintain, defend and enforce our patent rights, narrow the scope of our patent protection and, more generally, could affect the value or narrow the scope of our patent rights. For information relating to our patent portfolio, see Item 1 “Business—Intellectual Property”.

Moreover, we or our licensors may be subject to a third-party preissuance submission of prior art to the United States Patent and Trademark Office, or USPTO, or become involved in opposition, derivation, revocation, reexamination, inter partes review, post-grant 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 of, or invalidate, our patent rights, allow third parties to commercialize our technology or product candidates and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize drugs without infringing third-party patent rights. If the breadth or strength of protection provided by our patents and patent applications is threatened, regardless of the outcome, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates. For example, while we believe that the specific and generic claims contained in our issued and pending U.S. non-provisional and provisional applications provide protection for the pharmaceutical compositions and methods of use for pociredir, third parties may nevertheless challenge such claims. If any such claims are invalidated or rendered unenforceable for any reason, we will lose valuable intellectual property rights and our ability to prevent others from competing with us would be impaired.

Additionally, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Even if our owned and in-licensed patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and in-licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and product candidates. Such proceedings also may result in substantial cost and require significant time from our management and employees, even if the eventual outcome is favorable to us. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. Furthermore, our competitors may be able to circumvent our owned or in-licensed patents by developing similar or alternative technologies or products in a non-infringing manner. As a result, our owned and in-licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing technology and products similar or identical to any of our technology and product candidates.

Patent terms may be inadequate to protect our competitive position on our product candidates for an adequate amount of time.

Patents have a limited lifespan. In the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional filing date. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired, we may be open to competition from competitive products, including generics or biosimilars. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

If we are unable to obtain licenses from third parties on commercially reasonable terms or fail to comply with our obligations under such agreements, our business could be harmed.

It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our products, in which case we would be required to obtain a license from these third parties. If we are unable to license such technology, or if we are forced to license such technology on unfavorable terms, our business could be materially harmed. If we are unable to obtain a necessary license, we may be unable to develop or commercialize the affected product candidates, which could materially harm our business and the third parties owning such intellectual property rights could seek either an injunction prohibiting our sales or an obligation on our part to pay royalties and/or other forms of compensation. Even if we are able to obtain a license, it may be non-exclusive, thereby giving our competitors access to the same technologies licensed to us.

If we are unable to obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may be required to expend significant time and resources to redesign our technology, product candidates, or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize the affected technology and product candidates, which could harm our business, financial condition, results of operations and prospects significantly.

Additionally, if we fail to comply with our obligations under license agreements, our counterparties may have the right to terminate these agreements, in which event we might not be able to develop, manufacture or market, or may be forced to cease developing, manufacturing or marketing, any product that is covered by these agreements or may face other penalties under such agreements. Such an occurrence could materially adversely affect the value of the product candidate being developed under any such agreement. Termination of these agreements or reduction or elimination of our rights under these agreements, or restrictions on our ability to freely assign or sublicense our rights under such agreements when it is in the interest of our business to do so, may result in our having to negotiate new or reinstated agreements with less favorable terms, cause us to lose our rights under these agreements, including our rights to important intellectual property or technology or impede, or delay or prohibit the further development or commercialization of one or more product candidates that rely on such agreements.

Under our current license agreements, we may not have the final or sole decision on whether we are able to opt out certain of our in-licensed European patents and patent applications from the recently created Unified Patent Court, or the UPC, for the European Union. While our licensors have decided to opt out of the UPC, we cannot guarantee that our in-licensed European patents and patent applications will be challenged for non-compliance during the opt-out procedure and if successful, brought under the jurisdiction of the UPC, nor can we guarantee that our licensors will decide to opt back into the UPC at a later time. Thus, we cannot be certain that our in-licensed European patents and patent applications will not fall under the jurisdiction of the UPC. Under the UPC, a single European patent would be valid and enforceable in numerous European countries. A challenge to the validity of a European patent under the UPC, if successful, could result in a loss of patent protection in numerous European countries which could have a material adverse impact on our business and our ability to commercialize or license our technology and product candidates.

If we do not obtain patent term extension in the United States under the Hatch-Waxman Act and in foreign countries under similar legislation, our business may be materially harmed.

In the United States, the patent term of a patent that covers an FDA-approved drug may be eligible for limited patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to, among other factors, the length of time the drug is under regulatory review, but such patent extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, and only one eligible patent may be extended. Similar provisions are available in Europe and certain other jurisdictions outside the United States. If and when our

product candidate receives FDA approval, we expect to apply for patent term extensions where applicable, but there is no guarantee that the applicable governmental authorities will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such extensions. We may not be granted patent term extension either in the United States or in any foreign country because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. If we are unable to obtain any patent term extension or the term of any such extension is less than we request, our competitors may obtain approval of competing products following the expiration of our patent rights, and our business, financial condition, results of operations and prospects could be materially harmed.

Further, for our licensed patents, we may not have the right to control prosecution, including filing with the USPTO a petition for patent term extension thus if one of our licensed patents is eligible for patent term extension, we may not be able to control whether a petition to obtain a patent term extension is filed, or obtained, from the USPTO.

There are detailed rules and requirements regarding the patents that may be submitted to the FDA for listing in the Orange Book. We may be unable to obtain patents covering our product candidates that contain one or more claims that satisfy the requirements for listing in the Orange Book. Even if we submit a patent for listing in the Orange Book, the FDA may decline to list the patent, or a manufacturer of generic drugs may challenge the listing. If one of our product candidates is approved and a patent covering that product candidate is not listed in the Orange Book, an ANDA applicant would not have to provide notice to us with respect to that patent. See Item 1 "Business—Intellectual Property" for additional information regarding patent laws and patent protection.

Our issued European patents could be subject to the jurisdiction of the UPC.

Our European patents and patent applications could be challenged in the UPC. We decided to remove, i.e., opt out, our European patents and patent applications from the jurisdiction of the UPC. However, if certain formalities and requirements are not met, our European patents and patent applications could be challenged for non-compliance and brought under the jurisdiction of the UPC. We cannot be certain that our European patents and patent applications will avoid falling under the jurisdiction of the UPC. Under the UPC, a granted European patent would be valid and enforceable in numerous European countries. Although such patent rights would apply to numerous European countries, a successful challenge to a European patent under the UPC could result in loss of patent protection in numerous European countries. Accordingly, a single proceeding under the UPC addressing the validity and infringement of the European patent could result in loss of patent protection in numerous European countries rather than in each validated country separately as such patents always have been adjudicated. Such a loss of patent protection could have a material adverse impact on our business and our ability to commercialize or license our technology and product candidates.

Changes to patent laws in the United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products.

Changes in either the patent laws or interpretation of patent laws in the United States, including patent reform legislation such as the Leahy-Smith America Invents Act, or the Leahy-Smith Act, could increase the uncertainties and costs surrounding the prosecution of our owned and in-licensed patent applications and the maintenance, enforcement or defense of our owned and in-licensed issued patents. The Leahy-Smith Act includes a number of significant changes to United States patent law. These changes include provisions that affect the way patent applications are prosecuted, redefine prior art, provide more efficient and cost-effective avenues for competitors to challenge the validity of patents, and enable third-party submission of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent at USPTO-administered post-grant proceedings, including post-grant review, *inter partes* review, and derivation proceedings. Assuming that other requirements for patentability are met, prior to March 2013, in the United States, the first to invent the claimed invention was entitled to the patent, while outside the United States, the first to file a patent application was entitled to the patent. After March 2013, under the Leahy-Smith Act, the United States transitioned to a first-to-file system in which, assuming that the other statutory requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent on an invention regardless of whether a third party was the first to invent the claimed invention. As such, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

In addition, the patent positions of companies in the development and commercialization of biologics and pharmaceuticals are particularly uncertain. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. This combination of events has created uncertainty with respect to the validity and enforceability of patents once obtained. Depending on future actions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could have a material adverse effect on our patent rights and our ability to protect, defend and enforce our patent rights in the future.

Although we or our licensors are not currently involved in any litigation to protect or enforce our patent or other intellectual property rights, we may become involved in such lawsuits, which could be expensive, time-consuming and unsuccessful.

Competitors and other third parties may infringe, misappropriate or otherwise violate our or our licensor's issued patents or other intellectual property. As a result, we or our licensors may need to file infringement, misappropriation or other intellectual property related claims, which can be expensive and time-consuming. Any claims we assert against perceived infringers could provoke such parties to assert counterclaims against us alleging that we infringe, misappropriate or otherwise violate their intellectual property. In addition, in a patent infringement proceeding, such parties could counterclaim that the patents we or our licensors have asserted are invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity 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, or non-enablement. 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 institute such claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post-grant review, *inter partes* review, interference proceedings, derivation proceedings, and equivalent proceedings in foreign jurisdictions (*e.g.*, opposition proceedings). The outcome following legal assertions of invalidity and unenforceability is unpredictable.

An adverse result in any such proceeding could put one or more of our owned or in-licensed patents at risk of being invalidated or interpreted narrowly, and could put any of our owned or in-licensed patent applications at risk of not yielding an issued patent. A court may also refuse to stop the third party from using the technology at issue in a proceeding on the grounds that our owned or in-licensed patents do not cover such technology. 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 or trade secrets could be compromised by disclosure during this type of litigation. Any of the foregoing could allow such third parties to develop and commercialize competing technologies and products and have a material adverse impact on our business, financial condition, results of operations and prospects.

Interference or derivation 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. 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 or at all, or if a non-exclusive license is offered and our competitors gain access to the same technology. Our defense of litigation or interference or derivation 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.

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

Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing, misappropriating or otherwise violating the intellectual property and proprietary rights of third parties. There is considerable patent and other intellectual property litigation in the pharmaceutical and biotechnology industries. We may become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our technology and product candidates, including interference proceedings, post grant review, *inter partes* review, and derivation proceedings before the USPTO and similar proceedings in foreign jurisdictions such as oppositions before the European Patent Office. 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 pursuing development candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our technologies or product candidates that we may identify may be subject to claims of infringement of the patent rights of third parties.

The legal threshold for initiating litigation or contested proceedings is low, so that even lawsuits or proceedings with a low probability of success might be initiated and require significant resources to defend. Litigation and contested proceedings can also be expensive and time-consuming, and our adversaries in these proceedings may have the ability to dedicate substantially greater resources to prosecuting these legal actions than we can. The risks of being involved in such litigation

and proceedings may increase if and as our product candidates near commercialization and as we gain the greater visibility associated with being a public company. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future, regardless of merit. We may not be aware of all such intellectual property rights potentially relating to our technology and product candidates and their uses, or we may incorrectly conclude that third party intellectual property is invalid or that our activities and product candidates do not infringe such intellectual property. Thus, we do not know with certainty that our technology and product candidates, or our development and commercialization thereof, do not and will not infringe, misappropriate or otherwise violate any third party's intellectual property.

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations or methods, such as methods of manufacture or methods for treatment, related to the discovery, use or manufacture of the product candidates that we may identify or related to our technologies. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that the product candidates that we may identify may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. Moreover, as noted above, there may be existing patents that we are not aware of or that we have incorrectly concluded are invalid or not infringed by our activities. If any third-party patents were held by a court of competent jurisdiction to cover, for example, the manufacturing process of the product candidates that we may identify, any molecules formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block our ability to commercialize such product candidate unless we obtained a license under the applicable patents, or until such patents expire.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize the product candidates that we may identify. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure.

We may choose to take a license or, if we are found to infringe, misappropriate or otherwise violate a third party's intellectual property rights, we could also be required to obtain a license from such third party to continue developing, manufacturing and marketing our technology and product candidates. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors and other third parties access to the same technologies licensed to us and could require us to make substantial licensing and royalty payments. We could be forced, including by court order, to cease developing, manufacturing and commercializing the infringing technology or product. In addition, we could be found liable for significant monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent or other intellectual property right and could be forced to indemnify our customers or collaborators. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. In addition, we may be forced to redesign our product candidates, seek new regulatory approvals and indemnify third parties pursuant to contractual agreements. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar material adverse effect on our business, financial condition, results of operations and prospects.

Intellectual property litigation or other legal proceedings relating to intellectual property could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and may also have an advantage in such proceedings due to their more mature and developed intellectual property portfolios. Uncertainties resulting from the initiation and continuation of intellectual property litigation or other proceedings could compromise our ability to compete in the marketplace.

Obtaining and maintaining patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance, renewal and annuity fees and various other government fees on any issued patent and pending patent application must be paid to the USPTO and foreign patent agencies in several stages or annually over the lifetime of our owned and in-licensed patents and patent applications. The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. In certain circumstances, we rely on our licensing partners to pay these fees to, or comply with the procedural and documentary rules of, the relevant patent agency. With respect to our patents, we rely on an annuity service, outside firms and outside counsel to remind us of the due dates and to make payment after we instruct them to do so. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. In such an event, potential competitors might be able to enter the market with similar or identical products or technology. If we or our licensors fail to maintain the patents and patent applications covering our product candidates, it would have a material adverse effect on our business, financial condition, results of operations and prospects.

If we fail to comply with our obligations in our intellectual property licenses and funding arrangements with third parties, or otherwise experience disruptions to our business relationships with our licensors, we could lose intellectual property rights that are important to our business.

We are party to license and funding agreements, and we may enter into additional licensing and funding arrangements with third parties that impose or may impose diligence, development and commercialization timelines, milestone payment, royalty, insurance and other obligations on us. Under our existing licensing and funding agreements, we are obligated to pay royalties on net product sales of product candidates or related technologies to the extent they are covered by the agreements. If we fail to comply with such obligations under current or future license and funding agreements, our counterparties may have the right to terminate these agreements or require us to grant them certain rights. Such an occurrence could materially adversely affect the value of any product candidate being developed under any such agreement. Termination of these agreements or reduction or elimination of our rights under these agreements may result in our having to negotiate new or reinstated agreements with less favorable terms, or cause us to lose our rights under these agreements, including our rights to important intellectual property or technology, which would have a material adverse effect on our business, financial condition, results of operations and prospects. We also have licenses and agreements to certain technologies that we use in our discovery efforts, all of which are non-exclusive. While we still face all of the risks described herein with respect to those agreements, we cannot prevent third parties from also accessing those technologies. In addition, our licenses may place restrictions on our future business opportunities.

Disputes may arise regarding intellectual property subject to a licensing agreement, including:

- 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 under our collaborative development relationships;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the inventorship and ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and
- the priority of invention of patented technology.

In addition, the agreements under which we currently license intellectual property or technology from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could have a material adverse effect on our business, financial condition, results of operations and prospects. Moreover, if disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on commercially acceptable terms, we may be unable to successfully develop and commercialize the affected technology and product candidates, which could have a material adverse effect on our business, financial conditions, results of operations and prospects.

Our current or future licensors may have relied on third-party consultants or collaborators or on funds from third parties such that our licensors are not the sole and exclusive owners of the patents and patent applications we in-license. If other third parties have ownership rights to patents or patent applications we in-license, they may be able to license such patents to our competitors, and our competitors could market competing products and technology. This could have a material adverse effect on our competitive position, business, financial conditions, results of operations and prospects.

In spite of our best efforts, our licensors might conclude that we have materially breached our license agreements and might therefore terminate the license agreements, thereby removing our ability to develop and commercialize product candidates and technology covered by these license agreements. If these in-licenses are terminated, or if the underlying intellectual property fails to provide the intended exclusivity, competitors would have the freedom to seek regulatory approval of, and to market, products and technologies identical to ours. This could have a material adverse effect on our competitive position, business, financial condition, results of operations and prospects.

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

Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States, and even where such protection is nominally available, judicial and governmental enforcement of such intellectual property rights may be lacking. Consequently, we may not be able to prevent third parties from practicing our 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 or licenses but enforcement is not as strong as that in the United States. These products may compete with our products, 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 and in Russia, do not favor the enforcement of patents, trade secrets, and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our intellectual property and proprietary rights generally. In addition, certain jurisdictions do not protect to the same extent or at all inventions that constitute new methods of treatment.

Proceedings to enforce our intellectual property and proprietary 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, could put 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 and proprietary rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we or any of our licensors is forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be impaired, and our business, financial condition, results of operations and prospects may be adversely affected.

We may be subject to claims challenging the inventorship or ownership of our patents and other intellectual property.

We or our licensors may be subject to claims that former employees, collaborators or other third parties have an interest in our owned or in-licensed patents, trade secrets or other intellectual property as an inventor or co-inventor. For example, we or our licensors may have inventorship disputes arise from conflicting obligations of employees, consultants or others who are involved in developing our product candidates. Litigation may be necessary to defend against these and other claims challenging inventorship or our or our licensors' ownership of our owned or in-licensed patents, trade secrets or other intellectual property. If we or our licensors fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, intellectual property that is important to our product candidates. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

We may be subject to claims by third parties asserting that our employees, consultants or contractors have wrongfully used or disclosed confidential information of third parties, or we have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting we have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Many of our employees, consultants and contractors were previously employed at universities or other pharmaceutical or biotechnology companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and contractors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these individuals or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Litigation may be necessary to defend against these claims.

In addition, while it is our policy to require our employees, consultants and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own. Our intellectual property assignment agreements with them may not be self-executing or may be breached, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property. Such claims could have a material adverse effect on our business, financial conditions, results of operations and prospects.

If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could have a material adverse effect on our competitive business position and prospects. Such intellectual property rights could be awarded to a third party, and we could be required to obtain a license from such third party to commercialize our technology or products, which license may not be available on commercially reasonable terms, or at all, or such license may be non-exclusive. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to our management and employees.

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

In addition to seeking patents for our product candidates, we also rely on trade secrets and confidentiality agreements to protect our unpatented know-how, technology and other proprietary information, to maintain our competitive position, including certain aspects of our discovery technology. We seek to protect our trade secrets and other proprietary technology, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, CROs, CMOs, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants, but we cannot guarantee that we have entered into such agreements with each party that may have or has had access to our trade secrets or proprietary technology. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Detecting the disclosure or misappropriation of a trade secret and enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside of the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, 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. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third party, our competitive position would be materially and adversely harmed.

Intellectual property rights do not necessarily address all potential threats.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations and may not adequately protect our business or permit us to maintain our competitive advantage. For example:

- others may be able to make product candidates that are similar to ours but that are not covered by the claims of the patents that we own;
- we, or our license partners or current or future collaborators, might not have been the first to make the inventions covered by the issued patent or pending patent applications that we license or may own in the future;
- we, or our license partners or current or future collaborators, might not have been the first to file patent applications covering certain of our or their inventions;

•others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our owned or in-licensed intellectual property rights;

•it is possible that our owned and in-licensed pending patent applications or those we may own or in-license in the future will not lead to issued patents;

•issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors;

•our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;

•we cannot ensure that any of our patents, or any of our pending patent applications, if issued, or those of our licensors, will include claims having a scope sufficient to protect our product candidate;

•we cannot ensure that any patents issued to us or our licensors will provide a basis for an exclusive market for our commercially viable product candidates or will provide us with any competitive advantages;

•we cannot ensure that our commercial activities or product candidates will not infringe upon the patents of others;

•we cannot ensure that we will be able to successfully commercialize our product candidates on a substantial scale, if approved, before the relevant patents that we own or license expire;

•portions of our discovery technology are protected by trade secrets, but much is not protected by intellectual property, including patents, trade secrets and know-how, and we may not be able to develop, acquire or in-license any patentable technologies or other intellectual property related to the unprotected portions of our discovery portfolio;

•we may not develop additional proprietary technologies that are patentable;

•the patents of others may harm our business; and

•we may choose not to file a patent in order to maintain certain trade secrets or know-how, and a third party may subsequently file a patent covering such intellectual property.

Should any of these events occur, they could have a material adverse effect on our business, financial condition, results of operations and prospects.

Risks Related to Regulatory Approval of our Product Candidates and Other Legal Compliance Matters

Even if we complete the necessary preclinical studies and clinical trials, the marketing approval process is expensive, time-consuming and uncertain, and we may not obtain approvals for the commercialization of some or all of our product candidates. If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to commercialize our product candidates, and our ability to generate revenue will be materially impaired.

Marketing approval of drugs in the United States requires the submission of a new drug application, or NDA, to the FDA and we are not permitted to market any drug candidate in the United States until we obtain approval of the NDA. An NDA must be supported by extensive clinical and preclinical data, as well as extensive information regarding pharmacology, chemistry, manufacturing and controls. We have not submitted an application for or received marketing approval for any of our product candidates in the United States or in any other jurisdiction.

We have only limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party clinical research organizations or other third-party consultants or vendors to assist us in this process. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information, including manufacturing information, to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use. If any of our product candidates receives marketing approval, the accompanying label may limit the approved use of our drug, which could limit sales of the product.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive, may take many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data is insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

If we experience delays in obtaining approval or if we fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenues will be materially impaired.

Disruptions at the FDA, the SEC and other government agencies caused by the change in presidential administration, funding shortages or potential funding shortages could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner, or otherwise prevent those agencies from performing normal business functions, which could negatively impact our business and our timelines.

The ability of the FDA to review and clear or approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, shifting policy priorities as a result of changes in the Presidential administration and political appointees tasked to oversee the agency, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of the SEC, and other government agencies on which our operations may rely is subject to the impacts of political events, which are inherently fluid and unpredictable. Currently, federal agencies in the United States are operating under a continuing resolution that is set to expire on March 14, 2025.

Disruptions at the FDA and other agencies may slow the time necessary for review and approval, which could adversely affect our business. For example, over the last several years, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical FDA, SEC and other government employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA and the SEC to timely review and process our submissions, which could have a material adverse effect on our business and our timelines.

We may not be able to obtain or maintain orphan drug designation or exclusivity for our product candidates and, even if we do, that exclusivity may not prevent the FDA or the EMA from approving other competing products.

Regulatory authorities in some jurisdictions, including the United States and European Union, may designate drugs for relatively small patient populations as orphan drugs. We may seek orphan drug designation for our other current and future product candidates.

Generally, if a product with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of market exclusivity, which precludes the FDA or the EMA from approving another marketing authorization application for the same drug for a certain time period. The applicable period is seven years in the United States and ten years in the European Union. The exclusivity period in the European Union can be reduced to six years at the end of the fifth year if it is determined that a product no longer meets the criteria for orphan designation, including if the product is sufficiently profitable so that market exclusivity is no longer justified. Proposed amendments to European Union regulations regarding orphan medicines are under consideration which, if approved, could reduce the ten-year marketing exclusivity period.

Orphan drug exclusivity may be lost if the FDA or EMA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition.

Even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because competing drugs containing a different active ingredient can be approved for the same condition. In addition, the FDA or the EMA can subsequently approve the same drug for the same condition if the FDA or the EMA concludes that the later drug is clinically superior to the first drug to obtain orphan drug exclusivity because it is shown to be safer, more effective or makes a major contribution to patient care. Moreover, if we pursue and obtain approval for the same product for another indication for which we are not entitled to or do not have orphan drug exclusivity, our period of orphan

exclusivity will not prevent third parties from obtaining approval for a competing drug containing the same active ingredient for use in this other, non-orphan indication. If that were to occur, the protection we derive from orphan exclusivity may be adversely affected.

Designation by the FDA, such as fast track or breakthrough therapy, may not lead to a faster development or regulatory review or approval process, and it does not increase the likelihood that our product candidates will receive marketing approval.

The FDA granted fast track designation to pociredir for the treatment of SCD, and we may seek fast track designation for some of our other product candidates as well as breakthrough therapy designation. If a drug is intended for the treatment of a serious or life-threatening condition and the drug demonstrates the potential to address unmet medical needs for this condition, the drug sponsor may apply for FDA fast track designation. The FDA has broad discretion whether or not to grant this designation, so even if we believe a particular product candidate is eligible for this designation, we cannot assure stockholders that the FDA would decide to grant it. Even with fast track designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw fast track designation if it believes that the designation is no longer supported by data from our clinical development program.

A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

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

Even if the FDA agrees that we may pursue an accelerated approval NDA submission, approval of the NDA is not assured, nor does submission of an accelerated approval NDA ensure that the product candidate will have a faster development or regulatory review process.

We may seek approval, as applicable, of our product candidates using the FDA's accelerated approval pathway. A product may be eligible for accelerated approval if it treats a serious condition, generally provides a meaningful advantage over available therapies, and demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, or IMM, that is reasonably likely to predict an effect on IMM or other clinical benefit (*i.e.*, an intermediate clinical endpoint).

Prior to seeking such accelerated approval, we will seek feedback from the FDA and otherwise evaluate our ability to seek and receive such accelerated approval.

There can be no assurance that, after feedback from FDA, we will continue to pursue or apply for accelerated approval or any other form of expedited development, review or approval, even if we initially decide to do so. Furthermore, if we decide to submit an application for accelerated approval or under another expedited regulatory designation, there can be no assurance that such submission or application will be accepted or that any expedited review or approval will be granted on a timely basis, or at all.

Moreover, as a condition of accelerated approval, the FDA likely would require that we perform adequate and well-controlled post-marketing clinical trials to confirm the product's clinical benefit. These confirmatory trials must be completed with due diligence. Under the Food and Drug Omnibus Reform Act of 2022, or FDORA, the FDA may require that a post-approval confirmatory study or studies be underway prior to approval or within a specified time period after the date of approval for a product granted accelerated approval. FDORA also requires sponsors to send updates to the FDA every 180 days on the status of such studies, including progress toward enrollment targets, and the FDA must promptly post this information publicly. FDORA also gives the FDA increased authority to withdraw approval of a drug or biologic granted accelerated approval on an expedited basis if the sponsor fails to conduct such studies in a timely manner, send the necessary updates to the FDA, or if such post-approval studies fail to verify the drug's predicted clinical benefit. Under FDORA, the FDA is empowered to take action, such as issuing fines, against companies that fail to conduct with due diligence any post-approval confirmatory study or submit timely reports to the agency on their progress. In addition, the FDA generally requires pre-approval of promotional materials for products under consideration for accelerated approval, which could adversely

impact the timing of the commercial launch of the product. Thus, even if we seek to utilize the accelerated approval pathway for a product candidate, we may not experience a faster development or regulatory review or approval process for that product. In addition, receiving accelerated approval does not assure that the product's accelerated approval will ultimately be converted to a traditional approval.

Failure to obtain marketing approval in foreign jurisdictions would prevent any product candidates from being marketed abroad.

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

Additionally, now that the United Kingdom is no longer part of the European Union, separate applications and procedures will be required to obtain regulatory approval for our products in the United Kingdom and the European Union. Any delay in obtaining, or an inability to obtain, any marketing approvals could prevent us from commercializing any product candidates in the United Kingdom and/or the European Union and restrict our ability to generate revenue and achieve and sustain profitability.

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

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such product, will be subject to continual requirements of and review by the FDA and other regulatory authorities. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, including the requirement to implement a REMS. If any of our product candidates receives marketing approval, the accompanying label may limit the approved use of our drug, which could limit sales of the product.

The FDA may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product, including the adoption and implementation of REMS. The FDA and other agencies, including the Department of Justice, or the DOJ, closely regulate and monitor the post-approval marketing and promotion of drugs to ensure they are marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. Violations of the FDCA and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription drugs may lead to investigations and enforcement actions alleging violations of federal and state healthcare fraud and abuse laws, as well as state consumer protection laws.

In addition, later discovery of previously unknown adverse events or other problems with our products, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may have various consequences, including:

- suspension of or restrictions on such products, manufacturers or manufacturing processes;
- restrictions and warnings on the labeling or marketing of a product;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;

•recall of products;

•fines, restitution or disgorgement of profits or revenues;

•suspension of any ongoing clinical trials;

•suspension or withdrawal of marketing approvals;

•damage to relationships with any potential collaborators;

•unfavorable press coverage and damage to our reputation;

•refusal to permit the import or export of our products;

•product seizure or detention;

•injunctions or the imposition of civil or criminal penalties; or

•litigation involving patients using our products.

Non-compliance with European Union requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with the European Union's or United Kingdom's requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

In addition, manufacturers of approved products and those manufacturers' facilities are required to comply with extensive FDA requirements, including ensuring that quality control and manufacturing procedures conform to cGMPs applicable to drug manufacturers. Additionally, under FDORA, sponsors of approved drugs and biologics must provide six months' notice to the FDA of any changes in marketing status, such as the withdrawal of a drug, and failure to do so could result in the FDA placing the product on a list of discontinued products, which would revoke the product's ability to be marketed. We will also be subject to other regulatory requirements, including submissions of safety and other post-marketing information and reports, registration and listing requirements, requirements regarding the distribution of samples to clinicians, and recordkeeping.

Our relationships with healthcare providers, physicians and third-party payors will be subject to applicable anti-kickback, fraud and abuse, false claims, transparency, health information privacy and security, and other healthcare laws and regulations, which, in the event of a violation, could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm, administrative burdens and diminished profits and future earnings.

If we obtain regulatory approval and commercialize any products, healthcare providers, physicians and third-party payors will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with healthcare providers, physicians and third-party payors may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute any products for which we obtain marketing approval. In addition, we may be subject to transparency laws and patient privacy regulation by U.S. federal and state governments and by governments in foreign jurisdictions in which we conduct our business. See Item 1 "Business—Government Regulation and Product Approvals—Health Care Law and Regulation."

The distribution of pharmaceutical products is subject to additional requirements and regulations, including extensive record-keeping, licensing, storage and security requirements intended to prevent the unauthorized sale of pharmaceutical products.

The scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform, especially in light of the lack of applicable precedent and regulations. Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations, including anticipated activities that would be conducted by our sales team, are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from participation in government funded healthcare programs.

Compliance with global privacy and data security requirements could result in additional costs and liabilities to us or inhibit our ability to collect and process data globally, and the failure to comply with such requirements could subject us to significant fines and penalties, which may have a material adverse effect on our business, financial condition or results of operations.

The legislative and regulatory framework for the collection, use, safeguarding, sharing, transfer and other processing of information worldwide is rapidly evolving and is likely to remain uncertain for the foreseeable future. Globally, virtually every jurisdiction in which we operate has established its own data security and privacy frameworks with which we must comply. For example, the collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the European Economic Area, or EEA, including personal health data, is subject to the European Union's General Data Protection Regulation, or EU GDPR. Following the withdrawal of the United Kingdom from the European Union, or Brexit, the EU GDPR has been incorporated into United Kingdom's laws, or UK GDPR, alongside the UK Data Protection Act 2018, and together with the EU GDPR, is referred to as GDPR.

Despite Brexit, the EU and UK GDPR remain largely aligned. Currently, the most impactful point of divergence relates to transfer mechanisms (i.e., the ability for companies in the European Union or the United Kingdom to transfer personal information to third countries, including the United States), because it requires us to implement a variety of different contractual clauses approved by European Union's or United Kingdom's regulators, and carry out transfer impact assessments to establish whether the third country can ensure essential equivalency. This complexity and the additional contractual burden increases our overall risk exposure, and may result in us needing to make strategic considerations around where EEA and UK personal data is stored and which service providers we can utilize for the processing of EEA and UK personal data.

There may be further divergence in the future, including with regard to administrative burdens. The UK Government has also now introduced a Data Protection and Digital Information Bill, or the UK Bill, into the UK legislative process. The aim of the UK Bill is to reform the UK's data protection regime following Brexit. If passed, the final version of the UK Bill may have the effect of further altering the similarities between the UK and EEA data protection regime. This may lead to additional compliance costs and could increase our overall risk exposure as we may no longer be able to take a unified approach across the European Union and the United Kingdom, and we will need to amend our processes and procedures to align with the new framework.

Similar data protection laws are either in place or under way in the United States. There are a broad variety of privacy and data security laws and regulations that may be applicable to our activities governing the collection, use, disclosure, and protection of health-related and other personal information (including, state data breach notification laws, health information and/or genetic privacy laws and federal and state consumer protection laws including Section 5 of the FTC Act, HIPAA, and the California Consumer Privacy Act, or CCPA). For example, the CCPA as amended by the California Privacy Rights Act, has created certain requirements for data use, sharing and transparency, and provides California residents certain rights concerning their personal information, such as access, correction, deletion and opt out of selling or sharing such data. More than a dozen other states have implemented privacy legislation similar to the CCPA or are preparing to implement their own regulatory frameworks. For example, Washington state's My Health My Data Act, which took effect in March 2024, expands the definition of consumer health data, affords consumers with privacy rights and creates a private right of action, which could generate litigation. A wide range of enforcement agencies at both the state and federal levels, such as the Federal Trade Commission and state Attorneys General have been increasingly aggressive in reviewing and enforcing privacy and data security-related consumer protection laws. Regulators and legislators in the U.S. are increasingly scrutinizing and restricting certain personal data transfers and transactions involving foreign countries. See Item 1 "Business –Government Regulation and Product Approvals" for more information.

Given the breadth and depth of changes in privacy, data protection and consumer protection obligations, preparing for and complying with these requirements is rigorous and time intensive and requires significant resources and ongoing review of our technologies, systems and practices, as well as those of any third-party collaborators, service providers, contractors or consultants that store, process or transfer personal data on our behalf. Compliance with the GDPR and other similar laws or regulations associated with the enhanced protection of certain types of sensitive data, such as healthcare data or other personal information from our clinical trials, could require us to change our business practices and put in place additional compliance mechanisms, may interrupt or delay our development, regulatory and commercialization activities and increase our cost of doing business. Any failure or perceived failure by us to comply with such laws and regulations could lead to government enforcement actions, private litigation and significant fines and penalties against us and could have a material adverse effect on our business, financial condition or results of operations. There is also the threat of consumer class actions related to these laws and the overall protection of personal data. Even if we are not determined to have violated these laws,

government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our reputation and our business.

Recently enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidate and affect the prices we may obtain for any products that are approved in the United States or foreign jurisdictions.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates for which we obtain marketing approval. The pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by legislative initiatives. Current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any FDA approved product. If reimbursement of our products is unavailable or limited in scope, our business could be materially harmed. See Item 1 "Business—Government Regulation and Product Approval—Pharmaceutical Insurance Coverage and Health Care Reform" for more information.

For example, the Inflation Reduction Act of 2022, among other things, allows for Centers for Medicare & Medicaid Services to negotiate prices for certain single-source drugs and biologics reimbursed under Medicare Part B and Part D, beginning with select high-cost drugs in 2026. The legislation subjects drug manufacturers to civil monetary penalties and a potential excise tax for offering a price that is not equal to or less than the price negotiated under the law or for taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part B and Part D whose price increases exceed inflation. Further, the legislation caps Medicare beneficiaries' annual out-of-pocket drug expenses at $2,000. The implementation of the IRA is currently subject to ongoing litigation challenging the constitutionality of the IRA's Medicare drug price negotiation program. The effect of Inflation Reduction Act of 2022 on our business and the healthcare industry in general is not yet known.

The continuing efforts of the government, insurance companies, managed care organizations and other payers of healthcare services to contain or reduce costs of healthcare may adversely affect:

- the demand for any of our product candidates, if approved;
- the ability to set a price that we believe is fair for any of our product candidates, if approved;
- our ability to generate revenues and achieve or maintain profitability;
- the level of taxes that we are required to pay; and
- the availability of capital.

We expect that these healthcare reforms, 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, new payment methodologies and additional downward pressure on the price that we receive for any approved product and/or the level of reimbursement physicians receive for administering any approved product we might bring to market. Reductions in reimbursement levels may negatively impact the prices we receive or the frequency with which our products are prescribed or administered. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors.

Governments outside of the United States tend to impose strict price controls, which may adversely affect our revenues, if any.

In countries outside of the United States, particularly the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially.

If we or any third-party manufacturers we engage now or in the future fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs or liabilities that could harm our business.

We and third-party manufacturers we engage now are, and any third-party manufacturers we may engage in the future will be, subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. Liability under certain environmental laws governing the release and cleanup of hazardous materials is joint and several and could be imposed without regard to fault. We also could incur significant costs associated with civil or criminal fines and penalties or become subject to injunctions limiting or prohibiting our activities for failure to comply with such laws and regulations.

Although we maintain general liability insurance as well as workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials.

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

Further, with respect to the operations of our current and any future third-party contract manufacturers, it is possible that if they fail to operate in compliance with applicable environmental, health and safety laws and regulations or properly dispose of wastes associated with our products, we could be held liable for any resulting damages, suffer reputational harm or experience a disruption in the manufacture and supply of our product candidates or products. In addition, our supply chain may be adversely impacted if any of our third-party contract manufacturers become subject to injunctions or other sanctions as a result of their non-compliance with environmental, health and safety laws and regulations.

We are subject to anti-corruption laws, as well as export control laws, customs laws, sanctions laws and other laws governing our operations. If we fail to comply with these laws, we could be subject to civil or criminal penalties, other remedial measures and legal expenses, be precluded from developing manufacturing and selling certain products outside the United States or be required to develop and implement costly compliance programs, which could adversely affect our business, results of operations and financial condition.

Our operations are subject to anti-corruption laws, including the U.K. Bribery Act 2010, or Bribery Act, the U.S. Foreign Corrupt Practices Act, or FCPA, and other anti-corruption laws that apply in countries where we do business and may do business in the future. The Bribery Act, FCPA and these other laws generally prohibit us, our officers, and our employees and intermediaries from bribing, being bribed or making other prohibited payments to government officials or other persons to obtain or retain business or gain some other business advantage. Compliance with the FCPA, in particular, is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA presents particular challenges in the pharmaceutical industry, because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials. Certain payments to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions.

We may in the future operate in jurisdictions that pose a high risk of potential Bribery Act or FCPA violations, and we may participate in collaborations and relationships with third parties whose actions could potentially subject us to liability under the Bribery Act, FCPA or local anti-corruption laws. In addition, we cannot predict the nature, scope or effect of future regulatory requirements to which our international operations might be subject or the manner in which existing laws might be administered or interpreted. If we expand our operations outside of the United States, we will need to dedicate additional resources to comply with numerous laws and regulations in each jurisdiction in which we plan to operate.

We are also subject to other laws and regulations governing our international operations, including regulations administered by the governments of the United Kingdom and the United States, and authorities in the European Union, including applicable export control regulations, economic sanctions on countries and persons, customs requirements and currency exchange regulations, collectively referred to as the Trade Control laws. In addition, various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. If we expand our presence outside of the United States, it will require us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing, or selling certain products and product candidates outside of the United States, which could limit our growth potential and increase our development costs.

There is no assurance that we will be completely effective in ensuring our compliance with all applicable anti-corruption laws, including the Bribery Act, the FCPA or other legal requirements, including Trade Control laws. If we are not in compliance with the Bribery Act, the FCPA and other anti-corruption laws or Trade Control laws, we may be subject to criminal and civil penalties, disgorgement and other sanctions and remedial measures, and legal expenses, which could have an adverse impact on our business, financial condition, results of operations and liquidity. The SEC also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions. Any investigation of any potential violations of the Bribery Act, the FCPA, other anti-corruption laws or Trade Control laws by United Kingdom, United States or other authorities could also have an adverse impact on our reputation, our business, results of operations and financial condition.

Our employees, independent contractors, consultants and vendors may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading, which could cause significant liability for us and harm our reputation.

We are exposed to the risk of fraud or other misconduct by our employees, independent contractors, consultants and vendors. Misconduct by these partners could include intentional failures to comply with FDA regulations or similar regulations of comparable foreign regulatory authorities, provide accurate information to the FDA or comparable foreign regulatory authorities, comply with manufacturing standards, comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, report financial information or data accurately or disclose unauthorized activities to us. Employee 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. This could include violations of HIPAA, other U.S. federal and state law, and requirements of non-U.S. jurisdictions, including the EU GDPR. We are also exposed to risks in connection with any insider trading violations by employees or others affiliated with us. It is not always possible to identify and deter employee 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 be in compliance with such laws, standards, regulations, guidance or codes of conduct. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions.

Our internal computer and information technology systems and infrastructure, or those of our collaborators or other contractors or consultants, may fail or suffer security compromises or breaches, which could result in a disruption of our product development programs.

Our internal computer and information technology systems and infrastructure and those of our CROs, collaborators, and other contractors or consultants upon which our business relies, are vulnerable to breakdown or damage or interruption or otherwise may sustain damage from computer viruses, unauthorized access, data breaches, phishing attacks, cybercriminals, system malfunction, natural disasters (including hurricanes and earthquakes), terrorism, war and telecommunication and electrical failures. Such systems and infrastructure are also vulnerable to service interruptions or to security compromises or breaches from inadvertent or intentional actions by our employees, CROs or other third-party vendors, contractors, consultants and/or business partners or other third parties, or from cyber-attacks by malicious third parties. Cyber-attacks are increasing in their frequency, sophistication and intensity, and have become increasingly difficult to detect. Cyber-attacks could include wrongful conduct by insider employees or vendors, hostile foreign governments, industrial espionage, wire fraud and other forms of cyber fraud or cyber-attacks, including the deployment of harmful malware, ransomware, denial-of-service attacks, unauthorized access to or deletion of files, phishing attacks and social engineering, business email compromise, and other means to affect service reliability and threaten the confidentiality, integrity and availability of information. We, and our third party service providers, have experienced cyber incidents in the past, and we cannot guarantee that the measures we take to prevent, detect and respond to cyber-attacks will be effective to prevent or remediate future incidents. If our cybersecurity measures or those of our service providers fail to protect against unauthorized access, attacks, compromise or the mishandling of data by our employees or contractors, then our reputation, customer trust, business, results of operations and financial condition could be adversely affected. Because the techniques used by threat actors who may attempt to penetrate and sabotage our computer systems or those of our collaborators or other contractors or consultants change frequently and may not be recognized until launched against a target, we may be unable to anticipate these techniques.

While we have not experienced any material system failure, accident, cyber-attack or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions. For example, the loss of clinical trial data from completed or future clinical trials 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 compromise or breach were to result in a loss of, damage to, unauthorized access, or misuse of our data, systems, infrastructure or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability (including in connection with or resulting from litigation or governmental investigations and enforcement actions), our competitive position could be harmed and the further development and commercialization of our product candidates could be delayed and our business could be otherwise adversely affected. We cannot be sure that our cyber insurance coverage will be adequate or sufficient to protect us from or to mitigate liabilities arising out of any such disruption in, or failure or security incident, breach, or compromise of our system or third-party systems.

Risks Related to Employee Matters and Managing Growth

Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.

We are highly dependent on the research and development, clinical, financial, operational and other business expertise of our executive officers, as well as the other principal members of our management, scientific and clinical teams. Although we have entered into employment offer letters with our executive officers, each of them may terminate their employment with us at any time. We do not maintain "key person" insurance for any of our executives or other employees. Recruiting and retaining qualified scientific, clinical, manufacturing, accounting, legal and sales and marketing personnel will also be critical to our success.

We have had recent executive transitions, including of our chief executive officer, chief financial officer, president of research and development, chief scientific officer, and chief medical officer. We cannot predict the likelihood, timing or effect of future transitions among our executive leadership. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize products. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. Even if we are successful in our efforts to replace our executive leadership, we cannot guarantee that we will not face similar turnover in the future. In addition, we rely on consultants and advisors, including scientific and clinical

advisors, to assist us in formulating our research and development and commercialization strategy. In August 2022 and September 2024, we announced a workforce reduction in our research and development function, which may make us a less attractive employer to future candidates. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. Our success as a public company also depends on implementing and maintaining internal controls and the accuracy and timeliness of our financial reporting. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited.

We expect to expand our development and regulatory capabilities and, if appropriate, potentially implement sales, marketing and distribution capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

As we continue to expand our pipeline, we expect that we will experience growth in the number of our employees and the scope of our operations, particularly in the areas of drug development, clinical, regulatory affairs and, if any of our product candidates receives marketing approval, sales, marketing and distribution. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

Risks Related to our Common Stock

Our executive officers, directors and principal stockholders, if they choose to act together, have the ability to control or significantly influence all matters submitted to stockholders for approval.

As of February 18, 2025, our executive officers and directors and our stockholders who owned more than 5% of our outstanding common stock in the aggregate beneficially owned shares representing approximately 71.3% of our capital stock. As a result, if these stockholders were to choose to act together, they would be able to control or significantly influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would control the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets.

This concentration of ownership control may:

•delay, defer or prevent a change in control;

•entrench our management and board of directors; or

•delay or prevent a merger, consolidation, takeover or other business combination involving us that other stockholders may desire.

Provisions in our corporate 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 directors and members of management.

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

•establish a classified board of directors such that only one of three classes of directors is elected each year;

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

•limit the manner in which stockholders can remove directors from our board of directors;

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

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

•limit who may call stockholder meetings;

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

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

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

If securities analysts do not publish or cease publishing research or reports or publish misleading, inaccurate or unfavorable research about our business or if they publish negative evaluations of our stock, the price and trading volume of our stock could decline.

The trading market for our common stock relies, in part, on the research and reports that industry or financial analysts publish about us or our business. There can be no assurance that existing analysts will continue to cover us or that new analysts will begin to cover us. There is also no assurance that any covering analyst will provide favorable coverage. Although we have obtained analyst coverage, if one or more of the analysts covering our business downgrade their evaluations of our stock or publish inaccurate or unfavorable research about our business, or provides more favorable relative recommendations about our competitors, the price of our stock could decline. If one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price and trading volume to decline.

The price of our common stock may be volatile and fluctuate substantially, which could result in substantial losses for our stockholders.

The trading price of our common stock has been, and is likely to continue to be volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. The stock market in general and the market for smaller biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. The market price for our common stock may be influenced by many factors, including:

•results of or developments in preclinical studies and clinical trials of our product candidates or those of our competitors or potential collaborators;

•our success in commercializing our products, if and when approved;

•the success of competitive products or technologies;

•regulatory or legal developments in the United States and other countries;

•developments or disputes concerning patent applications, issued patents or other intellectual property or proprietary rights;

•the recruitment or departure of key personnel;

•the level of expenses related to any of our product candidates or clinical development programs;

•the results of our efforts to discover, develop, acquire or in-license products, product candidates, technologies or data referencing rights, the costs of commercializing any such products and the costs of development of any such product candidates or technologies;

•actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;

•variations in our financial results or the financial results of companies that are perceived to be similar to us;

•changes in the structure of healthcare payment systems;

•market conditions in the pharmaceutical and biotechnology sectors;

•general economic, industry and market conditions; and

•the other factors described in this "Risk Factors" section.

In the past, following periods of volatility in the market price of a company's securities, securities class-action litigation has often been instituted against that company. Any lawsuit to which we are a party, with or without merit, may result in an unfavorable judgment. We also may decide to settle lawsuits on unfavorable terms. Any such negative outcome could result in payments of substantial damages or fines, damage to our reputation or adverse changes to our offerings or business practices. Such litigation may also cause us to incur other substantial costs to defend such claims and divert management's attention and resources. Furthermore, negative public announcements of the results of hearings, motions or other interim proceedings or developments could have a negative effect on the market price of our common stock.

A significant portion of our total outstanding shares are eligible to be sold into the market, which could cause the market price of our common stock to drop significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. Persons who were our stockholders prior to our initial public offering continue to hold a substantial number of shares of our common stock. If such persons sell, or indicate an intention to sell, substantial amounts of our common stock in the public market, the trading price of our common stock could decline.

In addition, we have filed or intend to file universal shelf registration statements (which allows us to offer and sell securities from time to time pursuant to one or more offerings at prices and terms to be determined at the time of sale) subject to an aggregate offering amount stated therein, as well as registration statements registering all shares of common stock that we may issue under our equity compensation plans or pursuant to equity awards made to newly hired employees outside of equity compensation plans. Such registered shares can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates.

We are a "smaller reporting company," and the scaled disclosure requirements applicable to smaller reporting companies may make our common stock less attractive to investors.

We are a "smaller reporting company," or SRC. For so long as we remain an SRC, we are permitted and intend to rely on certain scaled disclosure requirements that are applicable to other public companies that are not SRCs. These scaled disclosure requirements include:

•not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;

•not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements; and

•reduced disclosure obligations regarding executive compensation.

We may choose to take advantage of some or all of the available exemptions. We cannot predict whether investors will find our common stock less attractive if we rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

We have incurred and will continue to incur increased costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives and corporate governance practices.

As a public company we have incurred, and we will continue to incur significant legal, accounting and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of The Nasdaq Global Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to

devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs, particularly as we hire additional financial and accounting employees to meet public company internal control and financial reporting requirements, and will make some activities more time-consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance, which in turn could make it more difficult for us to attract and retain qualified members of our board of directors.

We are evaluating these rules and regulations, and cannot predict or estimate the amount of additional costs we may incur or the timing of such costs. These rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, we are required to furnish a report by our management on our internal control over financial reporting. However, while we remain an SRC, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we conduct a process each year to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, including through hiring additional financial and accounting personnel, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by Section 404. If we identify one or more material weaknesses in our internal control over financial reporting, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

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

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. As a result, capital appreciation, if any, of our common stock will be our stockholders' sole source of gain for the foreseeable future.

Our certificate of incorporation designates the state courts in the State of Delaware as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could discourage lawsuits against the company and our directors, officers and employees.

Our certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware (or, if the Court of Chancery of the State of Delaware does not have jurisdiction, the federal district court for the District of Delaware) will be the sole and exclusive forum for (1) any derivative action or proceeding brought on our behalf, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers, employees or stockholders to our company or our stockholders, (3) any action asserting a claim arising pursuant to any provision of the DGCL or as to which the DGCL confers jurisdiction on the Court of Chancery of the State of Delaware or (4) any action asserting a claim arising pursuant to any provision of our certificate of incorporation or bylaws (in each case, as they may be amended from time to time) or governed by the internal affairs doctrine. This exclusive forum provision will not apply to actions arising under the Securities Act or the Securities Exchange Act of 1934, as amended.

This exclusive forum provision may limit the ability of our stockholders to bring a claim in a judicial forum that such stockholders find favorable for disputes with us or our directors, officers or employees, which may discourage such lawsuits against us and our directors, officers and employees. Alternatively, if a court were to find the choice of forum provision contained in our certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could materially adversely affect our business, financial condition and operating results.

Item 1B. Unresolved Staff Comments.

Not applicable.

Item 1C. Cybersecurity

Cyber Risk Management and Strategy

At Fulcrum Therapeutics, we recognize the importance of assessing, identifying, and managing risks from cybersecurity threats. We have implemented a cybersecurity risk management process in accordance with our risk profile and business that is informed by industry standards and is integrated into our enterprise risk management process.

We leverage the support of third-party information technology and security providers, including for periodic security testing and risk assessments, as part of our risk management process, designed to identify, assess, and manage cybersecurity risks. We conduct employee cybersecurity training and maintain an incident response and notification plan designed to assist us in identifying, responding to, and recovering from cybersecurity incidents. Further, we regularly evaluate and update our existing cybersecurity policies and procedures as appropriate to continue to align them to our risk profile.

We have a process to assess the security practices of certain third-party vendors, including through the use of vendor security questionnaires, as appropriate.

Although risks from cybersecurity threats have to date not materially affected us, our business strategy, results of operations or financial condition, we have, from time to time, experienced threats to and breaches of our and our third party vendors' data and systems. For more information about these risks, please refer to the section entitled "Risk Factors" in this Annual Report on Form 10-K.

Governance Related to Cybersecurity Risks

Our Executive Director, IT & Operations, or Executive Director, who reports to the Chief Financial Officer, is responsible for the strategic leadership and direction of our cybersecurity program. With over 15 years of experience in information technology, the Executive Director works alongside individuals across other functions, such as legal and engineering, to establish and implement our cybersecurity strategy.

The Executive Director and our Chief Legal Officer participate in periodic discussions with other members of our management, including executive leadership, regarding implementation of our cybersecurity program, program enhancements, and relevant cyber risks or threats. Our Chief Legal Officer has received the National Association of Corporate Directors CERT Certificate in Cyber-Risk Oversight.

Our audit committee has oversight over cybersecurity risks. With the input of the executive team, the Executive Director provides annual presentations to the audit committee on our cyber program, including updates on security testing and assessments, cyber risks, and related cyber strategy as applicable. The management team will also update the full board of directors on matters related to cybersecurity as needed.

Additionally, we have implemented an enterprise risk management process, which addresses cyber risks. This process is led by our Chief Legal Officer and includes participation by the board of directors, as appropriate. Our Chief Legal Officer reports regularly on the enterprise risk management process to executive leadership and the audit committee.

Item 2. Properties.

Our principal facilities consist of office and laboratory space. We occupy approximately 28,731 square feet of office space in Cambridge, Massachusetts under a lease that currently expires in June 2028.

Item 3. Legal Proceedings.

On April 28, 2023, a class action complaint was filed in the United States District Court for the District of New Jersey against our company and current and former officers, or the Securities Action. On May 19, 2023, the Securities Action was transferred to the United States District Court for the District of Massachusetts, captioned *Celano v. Fulcrum Therapeutics, Inc*., et al., Case No. 1:23-cv-11125-IT. On July 31, 2023, the court appointed a lead plaintiff, who filed an amended complaint on September 29, 2023. The Securities Action alleges violations of Section 10(b) of the Exchange Act and Rule 10b-5 promulgated thereunder against all defendants and control person violations of Section 20(a) against the individuals, related to our February 2023 announcement that the FDA issued a clinical hold regarding the IND application for pociredir for the potential treatment of SCD. The Securities Action alleges that the defendants made misleading statements and omitted to disclose material information related to the clinical hold and seeks, among other things, compensatory damages in connection with an allegedly inflated stock price between March 3, 2022, and March 8, 2023, as well as attorneys' fees and

costs. On November 28, 2023, all defendants filed a motion to dismiss the Securities Action. Briefing was completed on the motion in February 2024, and the court held a hearing on the motion in September 2024. The motion to dismiss is currently pending. We intend to defend vigorously against this litigation.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

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

Market Information

Our common stock trades under the symbol "FULC" on the Nasdaq Global Market and has been publicly traded since July 18, 2019. Prior to this time, there was no public market for our common stock.

Holders of Our Common Stock

As of February 18, 2025, there were approximately 11 holders of record of shares of our common stock. This number does not include stockholders for whom shares are held in "nominee" or "street" name.

Dividends

We have never declared or paid any cash dividends on our capital stock. We currently intend to retain all available funds and any future earnings for use in the operation of our business and do not anticipate paying any dividends on our common stock in the foreseeable future. Any future determination to declare dividends will be made at the discretion of our board of directors and will depend on our financial condition, operating results, capital requirements, general business conditions and other factors that our board of directors may deem relevant.

Unregistered Sales of Equity Securities

None.

Item 6. Reserved.

Not applicable.

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

The following discussion and analysis of our financial condition and results of operations should be read together with our consolidated financial statements and related notes appearing at the end of this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the "Risk Factors" section of this Annual Report on Form 10-K, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a clinical-stage biopharmaceutical company focused on developing small molecules to improve the lives of patients with genetically defined rare diseases in areas of high unmet medical need. Our clinical-stage product candidate, pociredir, is being developed for the potential treatment of sickle cell disease, or SCD.

In January 2023, we announced interim data from our Phase 1b clinical trial of pociredir in SCD. We completed enrollment in the 6 mg and 2 mg dose cohorts, and do not plan to enroll additional subjects in these cohorts. Although we commenced enrollment in the 12 mg dose cohort, in February 2023 the FDA placed a full clinical hold on the investigational new drug, or IND, application for pociredir for SCD, which was lifted in August 2023. Following the clinical hold, we amended the protocol to revise the inclusion and exclusion criteria for the Phase 1b clinical trial to target subjects with higher disease severity. We reinitiated the Phase 1b clinical trial at the 12 mg once daily dose level in the fourth quarter of 2023, with that cohort expected to enroll approximately 10 subjects, to be followed by an additional cohort of approximately 10 subjects at the 20 mg once daily dose level. Subjects are evaluated over a 12-week treatment period. We have enrolled 10 patients in the 12 mg dose cohort, and we expect to provide clinical data from the 12 mg dose cohort in mid-2025 and from the 20 mg dose cohort by the end of 2025.

In September 2024, we announced topline results from our Phase 3 REACH clinical trial of losmapimod in facioscapulohumeral muscular dystrophy, or FSHD. The Phase 3 REACH trial did not achieve its primary endpoint of change from baseline in relative surface area with losmapimod compared to placebo. In addition, secondary endpoints did not achieve nominal statistical significance. The safety and tolerability profile of losmapimod was consistent with previously reported studies. We plan to share the results at an upcoming medical meeting. Based on the results of the REACH trial, we have suspended future development of losmapimod.

In September 2024, we also announced a strategic plan to reprioritize research and development activities and are now focused on advancing pociredir for the treatment of SCD, novel therapeutic agents for the potential treatment of inherited aplastic anemias, such as DBA, Shwachman-Diamond syndrome, and Fanconi anemia, and our other discovery programs. The plan reduced our workforce from 80 to 51 full-time employees, including a reduction of positions across both research and development and general and administrative functions. We estimate that this restructuring will result in annual operating expense savings of approximately $10.0 million beginning in the first quarter of 2025.

In addition to our product candidates, we developed a discovery approach that we employ to systematically identify and validate cellular drug targets that can potentially modulate gene expression to treat known root causes of genetically defined rare diseases. Our discovery approach led to the identification of pociredir for SCD, as well as other drug candidates. We continue to advance our program for the potential treatment of inherited aplastic anemias, such as DBA, Shwachman-Diamond syndrome, and Fanconi anemia, and we plan to submit an IND for DBA during the fourth quarter of 2025.

Since inception, our operations have focused on organizing and staffing our company, business planning, raising capital, establishing our intellectual property, building our discovery platform, including our proprietary compound library and technologies, identifying drug targets and potential product candidates, in-licensing assets, producing drug substance and drug product material for use in clinical trials and conducting preclinical studies and clinical trials. To date, we have funded our operations primarily from the sale of shares of our capital stock and from upfront payments received under our collaboration and license agreements.

We have incurred significant operating losses since our inception and we expect to continue to incur significant operating losses for the foreseeable future. Our ability to generate product revenue sufficient to achieve profitability, if ever, will depend heavily on the successful development and eventual commercialization of one or more of our product candidates. Our net losses were $9.7 million and $97.3 million for the years ended December 31, 2024 and 2023, respectively. As of December 31, 2024, we had an accumulated deficit of $519.4 million. We expect our expenses and operating losses will increase substantially over the next several years in connection with our ongoing activities, as we:

- continue our clinical development of pociredir;
- continue our ongoing preclinical studies;
- advance clinical-stage product candidates into later stage trials;

•pursue the discovery of drug targets for other genetically-defined rare diseases and the subsequent development of any resulting product candidates, including for the potential treatment of inherited aplastic anemias, such as DBA, Shwachman-Diamond syndrome, and Fanconi anemia under our license agreement with CAMP4;

•seek regulatory approvals for any product candidates that successfully complete clinical trials;

•scale up our manufacturing processes and capabilities, or arrange for a third party to do so on our behalf, to support our clinical trials of our product candidates and commercialization of any of our product candidates for which we obtain marketing approval;

•establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain regulatory approval and that we have not out-licensed;

•acquire or in-license products, product candidates, technologies and/or data referencing rights, such as our agreement with CAMP4;

•make any milestone payments to CAMP4 under our license agreement;

•maintain, expand, enforce, defend and protect our intellectual property;

•hire additional clinical, quality control and scientific personnel; and

•add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts and our operations as a public company.

As a result, we will need substantial additional funding to support our continuing operations and pursue our growth strategy. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations through a combination of equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. We may be unable to raise additional funds or enter into such other agreements or arrangements when needed on favorable terms, or at all. If we fail to raise capital or enter into such agreements as, and when, needed, we may have to significantly delay, scale back or discontinue the development and commercialization of one or more of our product candidates, or grant rights to develop and market our product candidates even if we would otherwise prefer to develop and market such product candidates ourselves.

Because of the numerous risks and uncertainties associated with drug development, we are unable to predict the timing or amount of increased expenses or the timing of when or if we will be able to achieve or maintain profitability. Even if we are able to generate product sales, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce or terminate our operations.

As of December 31, 2024, we had $241.0 million in cash, cash equivalents, and marketable securities. We believe that our existing cash, cash equivalents, and marketable securities as of December 31, 2024 will enable us to fund our operating expenses and capital expenditure requirements into at least 2027. We have based this estimate on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we expect. See "—Liquidity and Capital Resources."

Components of Results of Operations

Revenue

We have not generated any revenue from product sales and do not expect to generate revenue from the sale of products for several years, if at all. If our development efforts for our current or future product candidates are successful and result in marketing approval, we may generate revenue in the future from product sales. We cannot predict if, when or to what extent we will generate revenue from the commercialization and sale of our product candidates. We may never succeed in obtaining regulatory approval for any of our product candidates.

In May 2024, we entered into a collaboration and license agreement with Sanofi, pursuant to which we granted Sanofi an exclusive license under certain intellectual property rights to commercialize losmapimod, an oral small molecule for the treatment of FSHD outside of the United States.

During the year ended December 31, 2024, we recognized $80.0 million of revenue associated with the upfront license payment. During the year ended December 31, 2024, we recorded a $8.1 million reduction in research and development expenses in connection with global development activities for losmapimod. During the year ended December 31, 2024, we recognized no revenue associated with the Sanofi territory-specific manufacturing activities for losmapimod. As a result of the suspension of future development of losmapimod, and Sanofi's recent notification of termination for convenience, we do not expect to recognize additional revenues under the Sanofi collaboration agreement.

In July 2020, we entered into a collaboration and license agreement with MyoKardia, which we amended in April 2023 and again in July 2024, pursuant to which we granted to MyoKardia an exclusive worldwide license under certain intellectual property rights to research, develop, make, have made, use, have used, sell, have sold, offer for sale, have offered for sale, import, have imported, export, have exported, distribute, have distributed, market, have marketed, promote, have promoted, or otherwise exploit products directed against certain biological targets identified by us that are capable of modulating up to a certain number of genes of interest with relevance to certain genetically defined cardiomyopathies. MyoKardia was subsequently acquired by Bristol-Myers Squibb Company in November 2020. The primary goal of the collaboration is to identify and validate potential biological targets for further research, in order to support the development, manufacture and commercialization of product candidates by MyoKardia for the potential treatment of certain genetically defined cardiomyopathies. We satisfied our obligation to perform research services as of December 31, 2023.

Under the terms of the MyoKardia collaboration agreement, we received a $10.0 million upfront payment and a $2.5 million payment as prepaid research funding in July 2020. MyoKardia agreed to reimburse us for the costs of the research activities not covered by the prepaid research funding, up to a maximum amount of total research funding (including the prepaid research funding). Upon the achievement of specified preclinical, development and sales milestones, we will be entitled to preclinical milestone payments, development milestone payments and sales milestone payments of up to $298.5 million in the aggregate per target for certain potential cardiomyopathy gene targets, and of up to $150.0 million in the aggregate per target for certain other potential cardiomyopathy gene targets. To date, we have achieved a $2.5 million specified preclinical milestone. MyoKardia will also pay us tiered royalties ranging from a mid single-digit percentage to a low double-digit percentage based on MyoKardia's, and any of its affiliates' and sublicensees', annual worldwide net sales of products under the MyoKardia collaboration agreement directed against any identified target. The royalties are payable on a product-by-product basis during a specified royalty term, and may be reduced in specified circumstances.

For the year ended December 31, 2024 we recognized no collaboration revenue under the MyoKardia collaboration agreement. For the year ended December 31, 2023 we recognized $2.8 million of collaboration revenue under the MyoKardia collaboration agreement. As of December 31, 2024 and December 31, 2023, we have recorded no deferred revenue associated with the MyoKardia collaboration agreement. As of December 31, 2024, we had received $7.7 million of cost reimbursement payments and $2.5 million of milestone payments under the MyoKardia collaboration agreement. As of December 31, 2024, we recorded no unbilled accounts receivable related to reimbursable research and development costs under the MyoKardia collaboration agreement for activities performed during the three months ended December 31, 2024.

In the future, we may generate revenue from milestones and royalty payments under the MyoKardia collaboration agreement. We expect that our revenue may fluctuate from quarter-to-quarter and year-to-year as a result of the timing, amount, and achievement of milestones under the MyoKardia collaboration agreement.

We may also in the future enter into additional license or collaboration agreements for our product candidates or intellectual property, and we may generate revenue in the future from payments as a result of such license or collaboration agreements.

Operating Expenses

Research and Development Expenses

Research and development expenses represent costs incurred by us for the discovery, development, and manufacture of our product candidates and include:

- external research and development expenses incurred under agreements with contract research organizations, contract manufacturing organizations, and consultants;
- salaries, payroll taxes, employee benefits and stock-based compensation expenses for individuals involved in research and development efforts;
- laboratory supplies;
- costs related to compliance with regulatory requirements; and
- facilities, depreciation and other allocated expenses, which include direct and allocated expenses for rent, maintenance of facilities, insurance and other operating costs.

We expense research and development costs as incurred. We recognize expenses for certain development activities, such as clinical trials and manufacturing, based on an evaluation of the progress to completion of specific tasks using data such as patient enrollment or other information provided to us by our vendors. Payments for these activities are based on the terms of the individual agreements, which may differ from the pattern of expenses incurred. Non-refundable advance payments for goods or services to be received in the future for use in research and development activities are recorded as

prepaid expenses. These amounts are recognized as an expense as the goods are delivered or the related services are performed, or until it is no longer expected that the goods will be delivered or the services rendered.

External costs represent a significant portion of our research and development expenses, which we track on a program-by-program basis following the nomination of a development candidate. Our internal research and development expenses consist primarily of personnel-related expenses, including stock-based compensation expense. We do not track our internal research and development expenses on a program-by-program basis as the resources are deployed across multiple projects.

The following table summarizes our external research and development expenses by program for the years ended December 31, 2024 and 2023. Pre-development candidate expenses, unallocated expenses and internal research and development expenses are classified separately. Payments to or reimbursements from Sanofi related to global development activities are accounted for as an increase to or reduction of losmapimod external expenses.

	Year Ended December 31,	
(in thousands)	**2024**	**2023**
Losmapimod external expenses	$ 20,801	$ 29,069
Pociredir external expenses	8,577	7,442
Pre-development candidate expenses and unallocated expenses	14,008	14,536
Internal research and development expenses	20,000	20,754
Total research and development expenses	$ 63,386	$ 71,801

The successful development of our product candidates is highly uncertain. At this time, we cannot reasonably estimate or know the nature, timing, and estimated costs of the efforts that will be necessary to complete the remainder of the development of our product candidates. We are also unable to predict when, if ever, material net cash inflows will commence from our product candidates, if approved. This is due to the numerous risks and uncertainties associated with developing our product candidates, including the uncertainty related to:

- the timing and progress of preclinical and clinical development activities;
- the number and scope of preclinical and clinical programs we decide to pursue;
- our ability to raise additional funds necessary to complete clinical development of and, if applicable, commercialize our product candidates if and when approved;
- our ability to maintain our current research and development programs and to establish new ones;
- our ability to establish new licensing or collaboration arrangements;
- the progress of the development efforts of parties with whom we may enter into collaboration arrangements;
- the successful initiation and completion of clinical trials with safety, tolerability and efficacy profiles that are satisfactory to the FDA or any comparable foreign regulatory authority;
- the receipt and related terms of regulatory approvals from applicable regulatory authorities;
- the availability of raw materials and active pharmaceutical ingredient, or API, for use in production of our product candidates;
- our ability to establish and operate a manufacturing facility, or secure manufacturing supply through relationships with third parties;
- our ability to consistently manufacture our product candidates in quantities sufficient for use in clinical trials;
- our ability to obtain and maintain intellectual property protection and regulatory exclusivity, both in the United States and internationally (including defending and enforcing our rights);
- our ability to obtain and maintain third-party coverage and adequate reimbursement for our product candidates, if approved;
- the acceptance of our product candidates, if approved, by patients, the medical community and third-party payors;
- competition with other products; and
- a continued acceptable safety profile of our products following receipt of any regulatory approvals.

A change in the outcome of any of these variables with respect to the development of any of our product candidates would significantly change the costs and timing associated with the development of that product candidate, and potentially other candidates.

Research and development activities account for a significant portion of our operating expenses. We expect our research and development expenses to increase in future periods as we continue to implement our business strategy, which includes advancing pociredir for the treatment of SCD, expanding our research and development efforts, including hiring additional personnel to support our research and development efforts, and seeking regulatory approvals for our product candidates that successfully complete clinical trials. In addition, product candidates in later stages of clinical development generally incur higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. As a result, we expect our research and development expenses to increase as our product candidates advance into later stages of clinical development. However, we do not believe that it is possible at this time to accurately project total program-specific expenses through approval and commercialization. There are numerous factors associated with obtaining regulatory approval and the successful commercialization of any of our product candidates, including future trial design and various regulatory requirements, many of which cannot be determined with accuracy at this time based on our stage of development.

General and Administrative Expenses

General and administrative expenses consist of personnel-related costs, including salaries, benefits and stock-based compensation expense, for our personnel in executive, finance and accounting, human resources, business operations and other administrative functions, legal fees related to patent, intellectual property and corporate matters, fees paid for accounting and tax services, consulting fees and facility-related costs not otherwise included in research and development expenses.

We expect that our general and administrative expenses will increase in the future to support continued research and development activities and planned commercialization activities, including establishing a sales, marketing and distribution infrastructure to commercialize any medicines for which we may obtain marketing approval. These increases will likely include increased costs related to the hiring of additional personnel, legal, audit, filing fees, and general compliance and consulting expenses, among other expenses.

Restructuring Expenses

In September 2024, we announced a plan to reprioritize research and development activities to focus on advancing pociredir for the treatment of SCD, novel therapeutic agents for the treatment of inherited aplastic anemias, such as DBA, Shwachman-Diamond syndrome, and Fanconi anemia, and our other discovery programs. The plan reduced our workforce from 80 to 51 full-time employees, including a reduction of positions across both research and development and general and administrative functions.

Other Income, Net

Other income, net consists primarily of interest income related to our investments in cash equivalents and marketable securities.

Results of Operations

Comparison of the Years Ended December 31, 2024 and 2023

The following summarizes our results of operations for the years ended December 31, 2024 and 2023, along with the changes in those items in dollars:

(in thousands)	Year Ended December 31, 2024	2023	Change $
Collaboration revenue	$ 80,000	$ 2,805	$ 77,195
Operating expenses:			
Research and development	63,386	71,801	(8,415)
General and administrative	36,448	41,668	(5,220)
Restructuring expense	2,063	—	2,063
Total operating expenses	101,897	113,469	(11,572)
Loss from operations	(21,897)	(110,664)	88,767
Other income, net	12,172	13,329	(1,157)
Net income (loss)	$ (9,725)	$ (97,335)	$ 87,610

Collaboration Revenue

Collaboration revenue increased by $77.2 million from $2.8 million for the year ended December 31, 2023 to $80.0 million for the year ended December 31, 2024. The increase was primarily attributable to the recognition of $80.0 million of revenue associated with the upfront license payment received during the year ended December 31, 2024 under the Sanofi collaboration agreement.

Research and Development Expenses

The following table summarizes our research and development expenses for the years ended December 31, 2024 and 2023:

(in thousands)	Year Ended December 31, 2024	2023	Change $
External research and development	$ 36,327	$ 41,179	$ (4,852)
Employee compensation	20,000	20,754	(754)
Laboratory supplies	1,528	3,501	(1,973)
Facility costs	4,483	4,834	(351)
Other	1,048	1,533	(485)
Total research and development expenses	$ 63,386	$ 71,801	$ (8,415)

Research and development expense decreased by $8.4 million from $71.8 million for the year ended December 31, 2023 to $63.4 million for the year ended December 31, 2024. The decrease in research and development expense was primarily attributable to the following:

- $4.9 million of decreased external research and development costs, primarily due to $8.1 million of reimbursement from the global development cost sharing under our collaboration with Sanofi for losmapimod, partially offset by increased development costs associated with the advancement of REACH, as we completed enrollment in September 2023, as well as increased costs associated with pociredir;
- $2.0 million of decreased laboratory costs;
- $0.8 million of decreased employee compensation costs due to decreased headcount, which reflects a partial offset of $0.9 million in increased stock-based compensation expense;
- $0.4 million of decreased facilities costs; and
- $0.5 million of decreased other costs.

General and Administrative Expenses

The following table summarizes our general and administrative expenses for the years ended December 31, 2024 and 2023:

(in thousands)	Year Ended December 31, 2024	2023	Change $
Employee compensation	$ 19,754	$ 24,809	$ (5,055)
Professional services	11,999	11,023	976
Facility costs	1,483	2,516	(1,033)
Other	3,212	3,320	(108)
Total general and administrative expenses	$ 36,448	$ 41,668	$ (5,220)

General and administrative expenses decreased by $5.3 million from $41.7 million for the year ended December 31, 2023 to $36.4 million for the year ended December 31, 2024. The decrease in general and administrative expenses was primarily attributable to the following:

- $5.1 million of decreased employee compensation costs due to decreased headcount, including a $1.1 million decrease in stock-based compensation expense;
- $1.0 million of decreased facility costs primarily as a result of the expiration of our lease agreement for office space at 125 Sidney Street; and
- $0.1 million in decreased other costs;
- partially offset by $1.0 million in increased professional services costs, primarily due to increased legal and commercial costs.

Other Income, Net

Other income, net decreased by $1.1 million from $13.3 million for the year ended December 31, 2023 to $12.2 million for the year ended December 31, 2024. The decrease in other income, net was primarily attributable to a decrease in our average cash, cash equivalents, and marketable securities balance.

Liquidity and Capital Resources

Sources of Liquidity

We have incurred significant operating losses since our inception and expect to continue to incur significant operating losses for the foreseeable future and may never become profitable. We have not yet commercialized any of our product candidates, which are in various phases of preclinical and clinical development, and we do not expect to generate revenue from sales of any products for several years, if at all. As of December 31, 2024, we have funded our operations primarily with aggregate gross proceeds of $792.5 million from the sale of shares of our capital stock and from upfront payments received under our collaboration and license agreements. As of December 31, 2024, we had cash, cash equivalents, and marketable securities of $241.0 million.

In February 2024, we entered into a controlled equity offering[SM] agreement with Cantor Fitzgerald & Co. and Stifel, Nicolaus & Company, Incorporated, as agents, with respect to an at-the-market offering program pursuant to which we may offer and sell, from time to time in our sole discretion, shares of our common stock, par value $0.001 per share, having an aggregate offering price of up to $100.0 million through the agents. As of December 31, 2024, we have not issued or sold any shares of common stock under the at-the-market offering program.

Cash Flows

The following table provides information regarding our cash flows for the years ended December 31, 2024 and 2023:

(in thousands)	Year Ended December 31, 2024	2023
Net cash used in operating activities	$ (2,218)	$ (90,965)
Net cash provided by (used in) investing activities	32,230	(36,692)
Net cash provided by financing activities	2,746	118,122
Net increase (decrease) in cash, cash equivalents, and restricted cash	$ 32,758	$ (9,535)

Net Cash Used in Operating Activities

Net cash used in operating activities was $2.2 million during the year ended December 31, 2024 compared to $91.0 million during the year ended December 31, 2023. The decrease in net cash used in operating activities of $88.8 million was primarily due to the receipt of the $80.0 million upfront license payment during the year ended December 31, 2024 under the Sanofi collaboration agreement.

Net Cash Provided by (Used in) Investing Activities

Net cash provided by investing activities was $32.2 million during the year ended December 31, 2024 compared to net cash used in investing activities of $36.7 million during the year ended December 31, 2023. The increase in net cash provided by investing activities of $68.9 million was primarily due to net maturities of marketable securities during the year ended December 31, 2024, as compared to net purchases of marketable securities during the year ended December 31, 2023.

Net Cash Provided by Financing Activities

Net cash provided by financing activities was $2.7 million during the year ended December 31, 2024 compared to $118.1 million during the year ended December 31, 2023. Net cash provided by financing activities during the year ended December 31, 2024 consisted of net proceeds of $2.7 million from the issuance of common stock under our benefit plans. Net cash provided by financing activities during the year ended December 31, 2023 primarily consisted of net proceeds of $117.3 million from the January 2023 public offering of our common stock.

Funding Requirements

We expect our expenses to increase substantially in connection with our ongoing research and development activities, particularly as we continue the research and development of, initiate clinical trials of, and seek marketing approval for, our product candidates, some of which are in the discovery stage of development. In addition, we expect to incur additional costs to support the growth of our organization when appropriate. As a result, we expect to incur substantial operating losses and negative operating cash flows for the foreseeable future.

Based on our current operating plan, we believe that our existing cash, cash equivalents, and marketable securities as of December 31, 2024 will enable us to fund our operating expenses and capital expenditure requirements into at least 2027. However, we have based this estimate on assumptions that may prove to be wrong and we could exhaust our capital resources sooner than we expect.

Our funding requirements and timing and amount of our operating expenditures will depend largely on:

•the progress, costs and results of our clinical trials of pociredir;

•the scope, progress, costs and results of discovery research, preclinical development, laboratory testing and clinical trials for our current product candidates in additional indications or for any future product candidates that we may pursue, including under our license agreement with CAMP4;

•the number of and development requirements for other product candidates that we pursue;

•the costs, timing and outcome of regulatory review of our product candidates;

•our ability to enter into contract manufacturing arrangements for supply of API and manufacture of our product candidates and the terms of such arrangements;

•the success of our collaboration with MyoKardia;

•our ability to establish and maintain additional strategic collaborations, licensing or other arrangements and the financial terms of such arrangements;

•the payment or receipt of milestones, royalties and other collaboration-based revenues, if any;

•the costs and timing of future commercialization activities, including product manufacturing, sales, marketing and distribution, for any of our product candidates for which we may receive marketing approval and that we do not out-license to a third party;

•the amount and timing of revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval;

•the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property and proprietary rights and defending any intellectual property-related claims; and

•the extent to which we acquire or in-license other products, product candidates, technologies or data referencing rights.

A change in the outcome of any of these or other variables with respect to the development of any of our product candidates could significantly change the costs and timing associated with the development of that product candidate. We will need to continue to rely on additional financing to achieve our business objectives.

In addition to the variables described above, if and when any of our product candidates successfully complete development, we will incur substantial additional costs associated with regulatory filings, marketing approval, post-marketing requirements, maintaining our intellectual property rights, and regulatory protection, in addition to other commercial costs. We cannot reasonably estimate these costs at this time.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaboration arrangements, strategic alliances and marketing, distribution or licensing arrangements. We currently have no credit facility or committed sources of capital. To the extent that we raise additional capital through the future sale of equity securities, the ownership interests of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our existing common stockholders. If we raise additional funds through the issuance of debt securities, these securities could contain covenants that would restrict our operations. We may require additional capital beyond our currently anticipated amounts, and additional capital may not be available on reasonable terms, or at all. If we raise additional funds through collaboration arrangements, strategic alliances or marketing, distribution or licensing arrangements in the future, we may have to relinquish valuable rights to our technologies, future revenue streams or product candidates, or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Critical Accounting Policies and Estimates

Our management's discussion and analysis of our financial condition and results of operations are based on our consolidated financial statements, which have been prepared in accordance with generally accepted accounting principles in the United States. The preparation of these consolidated financial statements requires us to make judgments and estimates that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the consolidated financial statements, and the reported amounts of expenses during the reporting periods. Our estimates are based on our historical experience, known trends and events, and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities and amount of expense recognized that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions. We evaluate our estimates and assumptions on an ongoing basis. The effects of material revisions in estimates, if any, will be reflected in the consolidated financial statements prospectively from the date of change in estimates.

We believe that the accounting policies discussed below are critical to understanding our historical and future performance, as these policies relate to the most significant areas involving management's judgments and estimates. See Note 2 to our consolidated financial statements included elsewhere in this Annual Report on Form 10-K for a description of our other significant accounting policies.

Collaborative Arrangements

At contract inception, we analyze our collaboration arrangements to assess whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and are exposed to significant risks and rewards dependent on the commercial success of such activities, and therefore within the scope of the Financial Accounting Standards Board Accounting Standards Codification, or ASC, Topic 808, *Collaborative Arrangements*, or ASC 808. This assessment is performed on an ongoing basis throughout the collaboration based on changes in the responsibilities of the parties in the arrangement. For collaboration arrangements within the scope of ASC 808 that contain multiple elements, we first determine which elements of the collaboration are deemed to be within the scope of ASC 808 and which elements of the collaboration are more reflective of a vendor-customer relationship and are therefore within the scope of ASC 606, *Revenue from Contracts with Customers*, or ASC 606.

For elements of collaboration arrangements that are accounted for pursuant to ASC 808, an appropriate recognition method is determined and applied consistently, either by analogy to authoritative accounting literature or by applying a reasonable and rational policy election. We evaluate the income statement classification for presentation of amounts due from or owed to collaborators associated with multiple activities in a collaboration arrangement based on the nature of each separate activity. We have made an accounting policy election to account for research and development reimbursements received from our collaboration partner that are outside of the scope of ASC 606 as a reduction of research and development expenses to best reflect the economics and nature of the transaction in the context of the unit-of-account.

Revenue Recognition

We account for revenue recognition under ASC 606. We recognize revenue pursuant to ASC 606 when our customer obtains control of promised goods or services in an amount that reflects the consideration which we expect to receive in exchange for those goods or services.

At contract inception, once the contract is determined to be within the scope of ASC 606, we assess the goods or services promised within the contract and determine those that are performance obligations. We then determine the transaction price and allocate it to the identified performance obligations. As part of the accounting for these arrangements, we must use significant judgment to determine the number of performance obligations and the transaction price, including the determination of whether milestones or other variable consideration should be included in the transaction price.

We use judgment to determine whether milestones or other variable consideration should be included in the transaction price. As part of management's evaluation of the transaction price, we consider numerous factors, including whether the achievement of the milestones is outside of our control, contingent upon the efforts of others or subject to the risks of success. If we conclude it is probable that a significant revenue reversal would not occur, the associated milestone payment is included in the transaction price. Milestone payments that are based on the occurrence of events not within our control, such as regulatory approvals, are generally not considered probable of being achieved until the underlying events occur or the associated approvals are received. At the end of each reporting period, we re-evaluate the estimated variable consideration included in the transaction price and any related constraint, and if necessary, adjust the estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis in the period of adjustment. Changes to the constraint of variable consideration can have a material effect on the amount of revenue recognized in the period.

If the contract contains a single performance obligation, the entire transaction price is allocated to the single performance obligation. Contracts that contain multiple performance obligations require an allocation of the transaction price to each performance obligation on a relative standalone selling price basis, except for any variable consideration that meets the criteria to be allocated entirely to a single performance obligation or to a distinct service that forms part of a single performance obligation.

We recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied, either at a point in time or over time. If the performance obligation is satisfied over time, we recognize revenue based on the use of either an output or input method. The estimation of measure of progress is complex, involves significant judgment, and is affected by our estimates of the total costs required to complete the performance obligations, including the total internal personnel costs and external costs to be incurred. Changes in these estimates can have a material effect on our revenue recognition. If the entity does not satisfy a performance obligation over time, the related performance obligation is satisfied at a point in time by transferring the control of a promised good or service to a customer.

Accrued Research and Development Expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued expenses as of each balance sheet date. This process involves reviewing open contracts and purchase orders, communicating

with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. The significant estimates in our accrued research and development expenses include the costs incurred for services performed by our vendors in connection with research and development activities for which we have not yet been invoiced.

We base our expenses related to research and development activities on our estimates of the services received and efforts expended pursuant to quotes and contracts with vendors that conduct research and development on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the research and development expense. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid expense accordingly. Non-refundable advance payments for goods and services that will be used in future research and development activities are expensed when the activity has been performed or when the goods have been received rather than when the payment is made.

Although we do not expect our estimates to be materially different from amounts actually incurred, if our estimates of the status and timing of services performed differ from the actual status and timing of services performed, it could result in us reporting amounts that are too high or too low in any particular period. To date, there have been no material differences between our estimates of such expenses and the amounts actually incurred.

Stock-Based Compensation

We measure stock-based compensation expense related to all restricted stock awards, restricted stock units, and stock options based on the fair value of the award on the date of grant. We recognize compensation expense for these awards over the requisite service period, which is generally the vesting period of the respective award. Generally, we issue awards with only service-based vesting conditions and record the expense for these awards using the straight-line method. We have also granted certain stock-based awards with performance-based vesting conditions. We recognize compensation expense for awards with performance-based vesting conditions over the remaining service period using an accelerated attribution method when management determines that achievement of the performance condition is probable. At each reporting date, we evaluate if the achievement of a performance-based milestone is probable based on the expected satisfaction of the performance conditions.

We determine the fair value of restricted stock awards and restricted stock units based on the estimated fair value of our common stock on the date of grant, less any applicable purchase price. We estimate the fair value of stock options granted using the Black-Scholes option-pricing model. The determination of the grant date fair value of stock options using an option pricing model is affected principally by our estimated fair value of our common stock and requires management to make a number of other assumptions, including the expected term of the option, the estimated volatility of the underlying shares, the risk-free interest rate, and expected dividends. The assumptions used in the determination of the grant date fair value of stock options represent management's best estimates at the time of measurement. Given the lack of public market for our common stock prior to the closing of our IPO and a lack of company-specific historical and implied volatility data, we based the estimate of expected volatility on the historical volatility of a representative group of publicly traded companies for which historical information is available. The historical volatility is calculated based on a period of time commensurate with the assumption used for the expected term. We use the simplified method to calculate the expected term for all stock options. We utilize this method as we do not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term. The risk-free interest rate is based on a U.S. treasury instrument whose term is consistent with the expected term of the stock options. The expected dividend yield is assumed to be zero as we have never paid dividends and do not have current plans to pay any dividends on common stock.

In future periods, we expect stock-based compensation expense to increase, due in part to our existing unrecognized stock-based compensation expense and as we grant additional stock-based awards to continue to attract and retain our employees.

Income Taxes

We account for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the consolidated financial statements or in our tax returns. Under this method, deferred tax assets and liabilities are determined based on differences between the financial statement carrying amounts and the tax bases of the assets and liabilities using the enacted tax rates in effect in the years in which the differences are expected to reverse. A valuation allowance against deferred tax assets is recorded if, based on the weight of the available evidence, it is more likely than not that some or all of the deferred tax assets

will not be realized. Potential for recovery of deferred tax assets is evaluated by considering several factors, including estimating the future taxable profits expected, estimating future reversals of existing taxable temporary differences, considering taxable profits in carryback periods, and considering prudent and feasible tax planning strategies.

We account for uncertain tax positions using a more-likely-than-not threshold for recognizing and resolving uncertain tax positions. The evaluation of uncertain tax positions is based on factors including, but not limited to, changes in the law, the measurement of tax positions taken or expected to be taken in tax returns, the effective settlement of matters subject to audit, new audit activity, and changes in facts or circumstances related to a tax position. As of each balance sheet date, we did not have any uncertain tax positions.

Recently Issued Accounting Pronouncements

A description of recently issued accounting pronouncements that may potentially impact our financial position and results of operations is disclosed in Note 2 to our audited consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K.

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

Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our cash equivalents are in the form of money market funds that are invested in U.S. Treasury securities and our investments are in short-term marketable securities, such as corporate bonds and commercial paper. As of December 31, 2024, we had cash, cash equivalents, and marketable securities of $241.0 million. Interest income is sensitive to changes in the general level of interest rates; however, due to the nature of these investments, an immediate 10% change in interest rates would not have a material effect on the fair market value of our investment portfolio.

We are also exposed to market risk related to changes in foreign currency exchange rates. We contract with vendors that are located outside of the United States and certain invoices are denominated in foreign currencies. We are subject to fluctuations in foreign currency rates in connection with these arrangements. We do not currently hedge our foreign currency exchange rate risk. As of December 31, 2024, we had minimal or no liabilities denominated in foreign currencies.

Inflation generally affects us by increasing our cost of labor and clinical trial costs. We do not believe that inflation had a material effect on our business, financial condition or results of operations during the years ended December 31, 2024 and 2023.

Item 8. Financial Statements and Supplementary Data.

Our consolidated financial statements, together with the independent registered public accounting firm report thereon, are presented beginning on page F-1 of this Annual Report on Form 10-K.

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

None.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer (our principal executive officer) and our Chief Financial Officer (our principal financial officer), evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2024. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company's management, including its principal executive and principal financial officers, or persons performing similar functions, as appropriate to allow timely decisions regarding required disclosure. Our management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and our management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2024, our Chief Executive Officer and our Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Annual Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting for the company. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act as a process designed by, or under the supervision of, a company's principal executive officer and principal financial officer, or persons performing similar functions, and effected by a company's board of directors, management, and other personnel, 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 and includes those policies and procedures that:

- pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of a company's assets;
- provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that a company's receipts and expenditures are being made only in accordance with authorizations of a company's management and directors; and
- provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of a 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. Therefore, even those systems determined to be effective can provide only reasonable assurance with respect to financial statement preparation and presentation. 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.

Under the supervision of and with the participation of our principal executive officer and principal financial officer, our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2024 based on the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in Internal Control—Integrated Framework (2013 framework). Based on this assessment, management concluded that our internal control over financial reporting was effective as of December 31, 2024.

Changes in Internal Control over Financial Reporting

There was no change in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) that occurred during the three months ended December 31, 2024 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

a)None.

b)Director and Officer Trading Plans and Arrangements.

On December 26, 2024, Alex C. Sapir, our President and Chief Executive Officer, adopted a trading plan for the potential sale of up to 360,000 shares of our common stock and for the potential exercise of vested stock options and the associated sale of up to 360,000 shares of our common stock. The trading plan is intended to satisfy the affirmative defense conditions of Rule 10b5-1(c) under the Exchange Act and was expected to remain in effect until December 31, 2025. On January 16, 2025, Mr. Sapir modified such 10b5-1(c) plan, which extended the date from which sales may commence and the price at which sales may be made, as well as the expiration date, which is now May 15, 2026, as so amended.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections.

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

Except to the extent provided below, the information required by this Item 10 will be included in our Definitive Proxy Statement to be filed with the SEC, with respect to our 2025 Annual Meeting of Stockholders and is incorporated herein by reference.

We post our Code of Business Conduct and Ethics, which applies to our directors, officers and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions, in the "Corporate Governance" sub-section of the "Investor Relations" section (ir.fulcrumtx.com) of our corporate website at www.fulcrumtx.com. We intend to disclose on our website any amendments to, or waivers from, the Code of Business Conduct and Ethics that are required to be disclosed pursuant to the disclosure requirements of Item 5.05 of Form 8-K.

Item 11. Executive Compensation.

The information required by this Item 11 will be included in our Definitive Proxy Statement to be filed with the SEC with respect to our 2025 Annual Meeting of Stockholders and is incorporated herein by reference.

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

The information required by this Item 12 will be included in our Definitive Proxy Statement to be filed with the SEC with respect to our 2025 Annual Meeting of Stockholders and is incorporated herein by reference.

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

The information required by this Item 13 will be included in our Definitive Proxy Statement to be filed with the SEC with respect to our 2025 Annual Meeting of Stockholders and is incorporated herein by reference.

Item 14. Principal Accountant Fees and Services.

The information required by this Item 14 will be included in our Definitive Proxy Statement to be filed with the SEC with respect to our 2025 Annual Meeting of Stockholders and is incorporated herein by reference.

PART IV

Item 15. Exhibits and Financial Statement Schedules.

(1) Consolidated Financial Statements

The following documents are included on pages F-1 through F-31 attached hereto and are filed as part of this Annual Report on Form 10-K.

	Page
Report of Independent Registered Public Accounting Firm (PCAOB ID: 42)	F-2
Consolidated Balance Sheets	F-4
Consolidated Statements of Operations and Comprehensive Loss	F-5
Consolidated Statements of Stockholders' Equity	F-6
Consolidated Statements of Cash Flows	F-7
Notes to Consolidated Financial Statements	F-8

(2) Financial Statement Schedules

All financial statement schedules have been omitted because they are not applicable, not required, or the information required is shown in the consolidated financial statements or the notes thereto.

(3) Exhibits

The exhibits required by Item 601 of Regulation S-K and Item 15(b) of this Annual Report on Form 10-K are listed in the Exhibit Index immediately preceding the signature page of this Annual Report on Form 10-K. The exhibits listed in the Exhibit Index are incorporated by reference herein.

Item 16. Form 10-K Summary

None.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

	Page
Report of Independent Registered Public Accounting Firm (PCAOB ID: 42)	F-2
Consolidated Balance Sheets	F-4
Consolidated Statements of Operations and Comprehensive Loss	F-5
Consolidated Statements of Stockholders' Equity	F-6
Consolidated Statements of Cash Flows	F-7
Notes to Consolidated Financial Statements	F-8

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Fulcrum Therapeutics, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Fulcrum Therapeutics, Inc. (the Company) as of December 31, 2024 and 2023, the related consolidated statements of operations and comprehensive loss, stockholders' equity and cash flows for the years then ended, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2024 and 2023, and the results of its operations and its cash flows for the years then ended, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements 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 audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the 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 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 financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective, or complex judgments. The communication of the critical audit matter 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.

Accrued Research Contract Costs

Description of the Matter

As of December 31, 2024, the Company had recognized $3.6 million of Accrued external research and development expenses. Included within this amount were accrued costs for clinical and contract research organization activities. As discussed in Note 2 to the consolidated financial statements, the Company accrues external costs for clinical trial activities based upon estimates of the services received and related expenses incurred through the balance sheet date that have yet to be invoiced by research institutions and other vendors.

Auditing the Company's accruals for clinical trials is challenging due to the fact that information necessary to estimate the accruals is accumulated from multiple sources. In addition, in certain circumstances, the determination of the nature and extent of services that have been received during the reporting period requires judgment because the timing and pattern of vendor invoicing does not correspond to the progress of the studies or extent of services provided and there may be delays in invoicing from vendors.

How We Addressed the Matter in Our Audit	To evaluate the accrual for clinical expenses, our audit procedures included, among others, testing the completeness and accuracy of the underlying data used by management to determine the estimate. We corroborated the progress of research and development activities associated with clinical trials through discussion with the Company's research and development personnel that oversee the research and development activities. We inspected contracts, amendments and change orders with clinical research organizations, tested the completeness and accuracy of invoicing activity associated with the Company's contractual obligations, and compared management's data and assumptions to information received directly from third parties. In addition, we performed analytics over fluctuations in accruals and prepaids by vendor throughout the period subject to audit and compared subsequent invoices received from third parties to amounts accrued.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2017.

Boston, Massachusetts
February 25, 2025

Fulcrum Therapeutics, Inc.

Consolidated Balance Sheets

(In thousands, except share and per share amounts)

	December 31, 2024	December 31, 2023
Assets		
Current assets:		
Cash and cash equivalents	$ 58,212	$ 25,563
Marketable securities	182,809	210,658
Unbilled accounts receivable	2,096	537
Prepaid expenses and other current assets	6,806	5,441
Total current assets	249,923	242,199
Property and equipment, net	3,900	5,216
Operating lease right-of-use assets	5,684	7,176
Restricted cash	1,201	1,092
Other assets	10	2,011
Total assets	$ 260,718	$ 257,694
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 1,164	$ 2,757
Accrued expenses and other current liabilities	7,694	8,726
Operating lease liability, current	2,186	2,192
Total current liabilities	11,044	13,675
Operating lease liability, excluding current portion	6,443	8,629
Other liabilities, excluding current portion	197	197
Total liabilities	17,684	22,501
Commitments and contingencies (Note 11)		
Stockholders' equity:		
Preferred stock, $0.001 par value; 5,000,000 shares authorized; no shares issued or outstanding	—	—
Common stock, $0.001 par value; 200,000,000 shares authorized; 53,968,303 and 61,915,367 shares issued and outstanding as of December 31, 2024 and December 31, 2023, respectively	54	62
Additional paid-in capital	762,248	744,940
Accumulated other comprehensive gain (loss)	130	(136)
Accumulated deficit	(519,398)	(509,673)
Total stockholders' equity	243,034	235,193
Total liabilities and stockholders' equity	$ 260,718	$ 257,694

The accompanying notes are an integral part of these financial statements.

Fulcrum Therapeutics, Inc.

Consolidated Statements of Operations and Comprehensive Loss

(In thousands, except per share data)

	Year Ended December 31,	
	2024	**2023**
Collaboration revenue	$ 80,000	$ 2,805
Operating expenses:		
Research and development	63,386	71,801
General and administrative	36,448	41,668
Restructuring expenses	2,063	—
Total operating expenses	101,897	113,469
Loss from operations	(21,897)	(110,664)
Other income, net	12,172	13,329
Net loss	$ (9,725)	$ (97,335)
Net loss per share, basic and diluted	$ (0.16)	$ (1.59)
Weighted-average common shares outstanding, basic and diluted	61,984	61,310
Comprehensive loss:		
Net loss	$ (9,725)	$ (97,335)
Other comprehensive gain:		
Unrealized gain on marketable securities	266	661
Total other comprehensive gain	266	661
Comprehensive loss	$ (9,459)	$ (96,674)

The accompanying notes are an integral part of these financial statements.

Fulcrum Therapeutics, Inc.

Consolidated Statements of Stockholders' Equity

(In thousands, except share amounts)

	Common Stock Shares	Common Stock Amount	Additional Paid-In Capital	Accumulated Other Comprehensive Gain (Loss)	Accumulated Deficit	Total Stockholders' Equity
Balance at December 31, 2022	52,099,211	52	612,025	(797)	(412,338)	198,942
Issuance of common stock in connection with public offering, net of issuance costs	9,615,384	10	117,336	—	—	117,346
Issuance of common stock under employee benefit plans	182,628	—	777	—	—	777
Vesting of restricted stock awards	18,144	—	—	—	—	—
Stock-based compensation expense	—	—	14,802	—	—	14,802
Unrealized gain on marketable securities	—	—	—	661	—	661
Net loss	—	—	—	—	(97,335)	(97,335)
Balance at December 31, 2023	61,915,367	$ 62	$ 744,940	$ (136)	$ (509,673)	$ 235,193
Issuance of common stock under employee benefit plans	530,610	—	2,746	—	—	2,746
Vesting of restricted stock awards	22,326	—	—	—	—	—
Issuance of pre-funded warrants in exchange for common stock	(9,350,000)	(9)	9	—	—	—
Issuance of common stock pursuant to pre-funded warrant exercise	850,000	1	(1)	—	—	—
Stock-based compensation expense	—	—	14,554	—	—	14,554
Unrealized gain on marketable securities	—	—	—	266	—	266
Net loss	—	—	—	—	(9,725)	(9,725)
Balance at December 31, 2024	53,968,303	$ 54	$ 762,248	$ 130	$ (519,398)	$ 243,034

The accompanying notes are an integral part of these financial statements.

Fulcrum Therapeutics, Inc.

Consolidated Statements of Cash Flows

(In thousands)

	Year Ended December 31,	
	2024	**2023**
Operating activities		
Net loss	$ (9,725)	$ (97,335)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation expense	1,593	2,172
Stock-based compensation expense	14,554	14,802
Net accretion of discounts on marketable securities	(4,392)	(5,991)
Changes in operating assets and liabilities:		
Unbilled accounts receivable	(1,559)	(308)
Prepaid expenses and other current assets	(1,365)	(1,072)
Operating lease assets and liabilities	(700)	(715)
Other assets	2,001	94
Accounts payable	(1,593)	(853)
Accrued expenses and other liabilities	(1,032)	(825)
Deferred revenue	—	(934)
Net cash used in operating activities	$ (2,218)	$ (90,965)
Investing activities		
Purchases of marketable securities	(178,594)	(194,892)
Maturities of marketable securities	211,102	158,708
Purchases of property and equipment	(278)	(508)
Net cash provided by (used in) investing activities	32,230	(36,692)
Financing activities		
Proceeds from issuance of common stock in connection with public offerings, net of issuance costs	—	117,345
Proceeds from issuance of common stock under benefit plans, net	2,746	777
Net cash provided by financing activities	2,746	118,122
Net increase (decrease) in cash, cash equivalents and restricted cash	32,758	(9,535)
Cash, cash equivalents, and restricted cash, beginning of period	26,655	36,190
Cash, cash equivalents, and restricted cash, end of period	$ 59,413	$ 26,655
Supplemental cash flow information		
Cash paid for operating lease liabilities	$ 2,782	$ 3,333

The following table provides a reconciliation of the cash, cash equivalents, and restricted cash balances as of each of the periods shown above:

	December 31, 2024	**December 31, 2023**
Cash and cash equivalents	$ 58,212	$ 25,563
Restricted cash	1,201	1,092
Total cash, cash equivalents, and restricted cash	$ 59,413	$ 26,655

The accompanying notes are an integral part of these financial statements.

Fulcrum Therapeutics, Inc.

Notes to Consolidated Financial Statements

1. Nature of the Business and Basis of Presentation

Fulcrum Therapeutics, Inc. (the "Company" or "Fulcrum") was incorporated in Delaware on August 18, 2015. The Company is focused on developing small molecules to improve the lives of patients with genetically-defined rare diseases in areas of high unmet medical need.

The Company is subject to a number of risks similar to other companies in the biotechnology industry, including, but not limited to, risks of failure of preclinical studies and clinical trials, dependence on key personnel, protection of proprietary technology, reliance on third party organizations, risks of obtaining regulatory approval for any product candidate that it may develop, development by competitors of technological innovations, compliance with government regulations, and the need to obtain additional financing. Product candidates currently under development will require significant additional research and development efforts, including extensive preclinical and clinical testing, and regulatory approval, prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel infrastructure and extensive compliance-reporting capabilities. Even if the Company's development efforts are successful, it is uncertain when, if ever, the Company will realize significant revenue from product sales.

Basis of Presentation

The accompanying consolidated financial statements have been prepared in conformity with generally accepted accounting principles in the United States of America ("GAAP"). Any reference in these notes to applicable guidance is meant to refer to the authoritative GAAP as found in the Accounting Standards Codification ("ASC") and Accounting Standards Updates ("ASU") of the Financial Accounting Standards Board ("FASB").

Sales of Common Stock

In January 2023, the Company completed a public offering of its common stock and issued and sold 9,615,384 shares of common stock at a public offering price of $13.00 per share, resulting in net proceeds of $117.3 million after deducting underwriting discounts and commissions and offering expenses.

Liquidity

The Company has incurred recurring losses and negative cash flows from operations since inception and has primarily funded its operations with proceeds from the sale of shares of its capital stock and from upfront payments received from collaboration and license agreements. As of December 31, 2024, the Company had an accumulated deficit of $519.4 million. The Company expects its operating losses and negative operating cash flows to continue into the foreseeable future as it continues to expand its research and development efforts. The Company expects to finance its future cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements.

The Company expects that its cash, cash equivalents, and marketable securities will be sufficient to fund its operating expenses and capital expenditure requirements for at least 12 months from the date of issuance of these financial statements. However, the Company has based this estimate on assumptions that may prove to be wrong, and its operating plan may change as a result of many factors currently unknown to it. As a result, the Company could deplete its capital resources sooner than it currently expects. If the Company is unable to raise additional funds through equity or debt financings when needed, it may be required to delay, limit, reduce or terminate development or future commercialization efforts or grant rights to develop and market product candidates that it would otherwise prefer to develop and market itself.

2. Summary of Significant Accounting Policies

Principles of Consolidation

The accompanying consolidated financial statements include the accounts of the Company and its wholly-owned subsidiary, Fulcrum Therapeutics Securities Corp., which is a Massachusetts subsidiary created to buy, sell, and hold securities. All intercompany transactions and balances have been eliminated.

Use of Estimates

The preparation of financial statements in accordance with GAAP requires management to make certain estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities as of the date of the financial statements, and the reported amount of expenses during the reported periods. Estimates inherent in the preparation of these consolidated financial statements include, but are not limited to, estimates related to collaborative arrangements, revenue from contracts with customers, accrued expenses, stock-based compensation expense, and income taxes. The Company bases its estimates on historical experience and other market specific or other relevant assumptions it believes to be reasonable under the circumstances. On an ongoing basis, management evaluates its estimates as there are changes in circumstances, facts and experience. Actual results could differ from those estimates or assumptions.

Cash and Cash Equivalents

Cash equivalents are highly liquid investments that are readily convertible into cash with original maturities of three months or less when purchased. Cash equivalents include investments in money market funds that invest in U.S. Treasury obligations, and commercial paper. The Company maintains its bank accounts at major financial institutions.

Restricted Cash

Restricted cash represents cash held to secure a letter of credit associated with the Company's facility lease for its corporate headquarters.

Fair Value of Financial Instruments

The fair value of the Company's financial assets and liabilities reflects the Company's estimate of amounts that it would have received in connection with the sale of the assets or paid in connection with the transfer of the liabilities in an orderly transaction between market participants at the measurement date. In connection with measuring the fair value of its assets and liabilities, the Company seeks to maximize the use of observable inputs (market data obtained from sources independent from the Company) and to minimize the use of unobservable inputs (the Company's assumptions about how market participants would price assets and liabilities). The following fair value hierarchy is used to classify assets and liabilities based on the observable inputs and unobservable inputs used in order to value the assets and liabilities:

Level 1: Quoted prices in active markets for identical assets or liabilities. An active market for an asset or liability is a market in which transactions for the asset or liability occur with sufficient frequency and volume to provide pricing information on an ongoing basis.

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 based on the Company's assessment of the assumptions that market participants would use in pricing the asset or liability.

The Company's cash equivalents and marketable securities are carried at fair value and are classified according to the fair value hierarchy described above (Note 3). The cash equivalents and marketable securities are initially valued at the transaction price, and subsequently revalued at the end of each reporting period, utilizing third-party pricing services. The pricing services utilize industry standard valuation models, including both income and market-based approaches, to determine fair value.

Marketable Securities

The Company classifies securities with a remaining maturity when purchased of greater than three months as marketable securities. As of December 31, 2024, the Company's marketable securities consisted of investments in U.S. Treasury securities, government agency securities, and corporate bonds. Marketable securities are classified as current assets on the consolidated balance sheets if the marketable securities are available to be converted into cash to fund current operations.

Marketable debt securities classified as available-for-sale are carried at fair value with the unrealized gains and losses included in accumulated other comprehensive loss, which is a component of stockholders' equity, until such gains and losses are realized. Any premium arising at purchase is amortized to interest expense (a component of other income, net) over the period of the earliest call date, and any discount arising at purchase is accreted to interest income (a component of other income, net) over the life of the instrument. Realized gains and losses are determined using the specific identification method and are included in other income, net.

If any adjustment to fair value reflects a decline in value of the investment, the Company considers all available evidence to evaluate the extent to which the decline is "other-than-temporary" and, if so, marks the investment to market through a charge to the Company's statement of operations and comprehensive loss.

Property and Equipment

Property and equipment are recorded at cost, net of accumulated depreciation. Maintenance and repairs to an asset that do not improve or extend its life are charged to operations. Depreciation expense is recorded using the straight-line method over the estimated useful life of the related asset as follows:

	Estimated Useful Life (in years)
Lab equipment	5
Furniture and fixtures	4
Computer equipment	3
Software	3
Leasehold improvements	Shorter of useful life or remaining lease term

Construction-in-progress is stated at cost, which includes direct costs attributable to the setup or construction of the related asset. Depreciation expense is not recorded on construction-in-progress until the relevant assets are completed and put into use. When assets are retired or otherwise disposed of, the assets and related accumulated depreciation are eliminated from the accounts and any resulting gain or loss is reflected in the Company's consolidated statements of operations and comprehensive loss.

Impairment of Long-Lived Assets

Long-lived assets consist of property and equipment. The Company continually evaluates whether events or circumstances have occurred that indicate that the estimated remaining useful life of its long-lived assets may warrant revision or that the carrying value of these assets may be impaired. An impairment loss would be recognized when estimated undiscounted future cash flows expected to result from the use or disposition of an asset group are less than its carrying amount. The impairment loss would be based on the excess of the carrying value of the impaired asset group over its fair value, determined based on discounted cash flows. The Company did not record any impairment losses on long-lived assets during the years ended December 31, 2024 and 2023.

Leases

The Company accounts for its leases in accordance with ASC 842, *Leases*. At the inception of a contract, the Company determines whether the arrangement is or contains a lease based on the unique facts and circumstances present in the arrangement. Leases with a term greater than twelve months are recognized on the balance sheet as right-of-use assets and current and non-current lease liabilities, as applicable. The Company does not recognize leases with terms of twelve months or less on the balance sheet. Options to renew a lease are not included in the Company's initial lease term assessment unless there is reasonable certainty that the Company will renew the lease.

Leases are classified as either finance leases or operating leases. A lease is classified as a finance lease if any one of the following criteria are met: (i) the lease transfers ownership of the asset by the end of the lease term, (ii) the lease contains an option to purchase the asset that is reasonably certain to be exercised, (iii) the lease term is for a major part of the remaining useful life of the asset or (iv) the present value of the lease payments equals or exceeds substantially all of the fair value of the asset. A lease is classified as an operating lease if it does not meet any of these criteria.

For all operating leases, a lease liability and corresponding right-of-use asset are recognized. The lease liability represents the present value of the lease payments over the expected remaining lease term, discounted using the interest rate implicit in the lease or, if that rate cannot be readily determined, the Company's incremental borrowing rate, which reflects the fixed rate at which the Company could borrow on a collateralized basis the amount of the lease payments in the same

currency, for a similar term, in a similar economic environment. To estimate the Company's incremental borrowing rate, a credit rating applicable to the Company is estimated using a synthetic credit rating and yield curve analysis, since the Company does not have a rating agency-based credit rating. The right-of-use asset represents the right to use the leased asset for the lease term. The right-of-use asset is initially measured at cost, which primarily comprises the initial amount of the lease liability, plus any initial direct costs incurred if any, less any lease incentives received.

Lease payments included in the measurement of the lease liability comprise (i) the fixed noncancelable lease payments, (ii) payments for optional renewal periods where it is reasonably certain the renewal period will be exercised, and (iii) payments for early termination options unless it is reasonably certain the lease will not be terminated early. Lease expense for operating leases consists of the lease payments plus any initial direct costs, and is recognized on a straight-line basis over the lease term. Included in lease expense are any variable lease payments incurred in the period that are not included in the initial lease liability and lease payments incurred in the period for any leases with an initial term of 12 months or less. The Company accounts for lease and non-lease components together as a single lease component.

Common Stock Warrants

The Company accounts for common stock warrants as either equity-classified or liability-classified instruments based on an assessment of the warrant's specific terms and applicable authoritative guidance in ASC 480, *Distinguishing Liabilities from Equity* (ASC 480) and ASC 815, *Derivatives and Hedging* (ASC 815). The assessment considers whether the warrants are freestanding financial instruments pursuant to ASC 480, whether the warrants meet the definition of a liability pursuant to ASC 480, and whether the warrants meet all of the requirements for equity classification under ASC 815, including whether the warrants are indexed to the Company's own common stock and whether the warrant holders could potentially require "net cash settlement" in a circumstance outside of the Company's control, among other conditions for equity classification. This assessment, which requires the use of professional judgment, is conducted at the time of warrant issuance and as of each subsequent quarterly period end date while the warrants are outstanding.

For issued or modified warrants that meet all of the criteria for equity classification, the warrants are required to be recorded as a component of additional paid-in capital at the time of issuance. For issued or modified warrants that do not meet all the criteria for equity classification, the warrants are required to be recorded at their initial fair value on the date of issuance and remeasured each balance sheet date thereafter. Changes in the estimated fair value of the liability-classified warrants are recognized as a non-cash gain or loss in the accompanying consolidated statements of operations and comprehensive loss.

Collaborative Arrangements

At contract inception, the Company analyzes its collaboration arrangements to assess whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and are exposed to significant risks and rewards dependent on the commercial success of such activities, and therefore within the scope of ASC Topic 808, *Collaborative Arrangements* (ASC 808). This assessment is performed on an ongoing basis throughout the collaboration based on changes in the responsibilities of the parties in the arrangement. For collaboration arrangements within the scope of ASC 808 that contain multiple elements, the Company first determines which elements of the collaboration are deemed to be within the scope of ASC 808 and which elements of the collaboration are more reflective of a vendor-customer relationship and are therefore within the scope of ASC 606, *Revenue from Contracts with Customers* (ASC 606).

For elements of collaboration arrangements that are accounted for pursuant to ASC 808, an appropriate recognition method is determined and applied consistently, either by analogy to authoritative accounting literature or by applying a reasonable and rational policy election. The Company evaluates the income statement classification for presentation of amounts due from or owed to collaborators associated with multiple activities in a collaboration arrangement based on the nature of each separate activity. The Company made an accounting policy election to account for research and development reimbursements received from its collaboration partner that are outside of the scope of ASC 606 as a reduction of research and development expenses to best reflect the economics and nature of the transaction in the context of the unit-of-account.

Revenue Recognition

Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration that the entity expects to receive in exchange for those goods or services. In applying ASC 606, the Company performs the following five steps:

1) Identify the contract with the customer

A contract with a customer exists when (i) the Company enters into an enforceable contract with a customer that defines each party's rights regarding the goods or services to be transferred and identifies the related payment terms, (ii) the contract has commercial substance and (iii) the Company determines that collection of substantially all consideration for goods and services that are transferred is probable based on the customer's intent and ability to pay the promised consideration.

2) Identify the promises and performance obligations in the contract

Performance obligations promised in a contract are identified based on the goods and services that will be transferred to the customer that are both capable of being distinct, whereby the customer can benefit from the good or service either on its own or together with other readily available resources, and are distinct in the context of the contract, whereby the transfer of the good or service is separately identifiable from other promises in the contract. To the extent a contract includes multiple promised goods and services, the Company must apply judgment to determine whether promised goods and services are capable of being distinct and distinct in the context of the contract. In assessing whether a promised good or service is distinct, the Company considers factors such as the research, manufacturing and commercialization capabilities of the customer and the availability of the associated expertise in the marketplace. The Company also considers the intended benefit of the contract in assessing whether a promised good or service is separately identifiable from other promises in the contract. If these criteria are not met, the promised goods and services are accounted for as a combined performance obligation.

3) Determine the transaction price

The transaction price is determined based on the consideration to which the Company will be entitled in exchange for transferring goods and services to the customer. If the consideration promised in a contract includes a variable amount, the Company estimates the amount of consideration to which it will be entitled in exchange for transferring the promised goods or services to a customer. The Company determines the amount of variable consideration by using the expected value method or the most likely amount method. The Company includes the unconstrained amount of estimated variable consideration in the transaction price. The amount included in the transaction price is constrained to the amount for which it is probable that a significant reversal of cumulative revenue recognized will not occur. At the end of each subsequent reporting period, the Company re-evaluates the estimated variable consideration included in the transaction price and any related constraint, and if necessary, adjusts the estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis in the period of adjustment. Changes to the constraint of variable consideration can have a material effect on the amount of revenue recognized in the period.

If an arrangement includes research and development milestone payments, the Company evaluates whether the milestones are considered probable of being reached and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are based on the occurrence of events not within the Company's control, such as regulatory approvals, are generally not considered probable of being achieved until the underlying events occur or the associated approvals are received.

For arrangements with licenses of intellectual property that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Company recognizes royalty revenue and sales-based milestones at the later of (i) when the related sales occur, or (ii) when the performance obligation to which the royalty has been allocated has been satisfied.

In determining the transaction price, the Company adjusts consideration for the effects of the time value of money if the timing of payments provides the Company with a significant benefit of financing. The Company assesses its revenue generating arrangements in order to determine whether a significant financing component exists.

4) Allocate the transaction price to the performance obligations in the contract

If the contract contains a single performance obligation, the entire transaction price is allocated to the single performance obligation. Contracts that contain multiple performance obligations require an allocation of the transaction price

to each performance obligation on a relative standalone selling price basis, except for any variable consideration that meets the criteria to be allocated entirely to a single performance obligation or to a distinct service that forms part of a single performance obligation.

5) Recognize revenue when or as the Company satisfies a performance obligation

The Company may satisfy performance obligations over time or at a point in time, depending on the nature of the performance obligation. Revenue is recognized over time if the customer simultaneously receives and consumes the benefits provided by the entity's performance, the entity's performance creates or enhances an asset that the customer controls as the asset is created or enhanced, or the entity's performance does not create an asset with an alternative use to the entity and the entity has an enforceable right to payment for performance completed to date. If the entity does not satisfy a performance obligation over time, the related performance obligation is satisfied at a point in time by transferring the control of a promised good or service to a customer.

For revenue that the Company recognizes over time, the Company assesses whether an input or an output method is the appropriate measure of progress associated with the satisfaction of the performance obligation. In determining the appropriate method for measuring progress, the Company considers the nature of the good or service that it has promised to transfer to the customer. Output methods recognize revenue on the basis of direct measurements of the value to the customer of the goods or services transferred to date relative to the remaining goods or services promised under the contract. Input methods recognize revenue on the basis of the entity's efforts or inputs to the satisfaction of a performance obligation. Estimates inherent to the measurement of progress associated with the satisfaction of performance obligations based on an input method include the total estimated costs to satisfy the associated performance obligation.

Research and Development Expenses

Research and development expenses include costs directly attributable to the conduct of research and development programs, including personnel-related expenses such as salaries, payroll taxes, benefits, and stock-based compensation expense, manufacturing and external costs related to outside vendors engaged to conduct both preclinical studies and clinical trials, laboratory supplies, depreciation on and maintenance of research equipment, and the allocable portions of facility costs, such as rent, utilities, repairs and maintenance, depreciation, and general support services. Expenditures relating to research and development are expensed in the period incurred. Non-refundable advance payments for goods and services that will be used in future research and development activities are expensed when the activity has been performed or when the goods have been received rather than when the payment is made.

Research Contract Costs and Accruals

The Company has entered into various research and development contracts with research institutions and other companies. The Company records accruals for estimated ongoing research costs that have not yet been invoiced. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the studies or trials or the extent of services provided during the reporting periods, including invoices received and contracted costs. Significant judgments and estimates made in determining the accrued balances at each reporting period include the estimates of the time period over which services will be performed and the level of effort to be expended in each period that have yet to be invoiced by the vendors. Actual results could differ from the Company's estimates.

Patent-Related Costs

Patent-related costs incurred in connection with patent applications are expensed as incurred due to the uncertainty about the recovery of the expenditure. Amounts incurred are classified as general and administrative expenses in the accompanying statements of operations.

Stock-Based Compensation

The Company measures stock-based awards based on the fair value on the date of grant. Compensation expense associated with those awards is recognized over the requisite service period, which is generally the vesting period of the respective award. Generally, the Company issues awards with only service-based vesting conditions and records the expense for these awards using the straight-line method.

The fair value of each restricted stock award is based on the fair value of the Company's common stock on the grant date, less any applicable purchase price. The fair value of each stock option is estimated on the grant date using the Black-Scholes option-pricing model, which requires inputs based on certain subjective assumptions, including the expected stock

price volatility, the expected term of the award, the risk-free interest rate, and expected dividends. Expected volatility is calculated based on reported volatility data for a representative group of publicly traded companies for which historical information is available. The historical volatility is calculated based on a period of time commensurate with the assumption used for the expected term. The risk-free interest rate is based on the U.S. Treasury yield curve in effect at the time of grant commensurate with the expected term assumption. The Company uses the simplified method, under which the expected term is presumed to be the midpoint between the vesting date and the end of the contractual term. The Company utilizes this method due to the lack of historical exercise data and the plain nature of its stock-based awards. The expected dividend yield is assumed to be zero as the Company has never paid dividends and has no current plans to pay any dividends on common stock.

The Company accounts for forfeitures as they occur. The Company classifies stock-based compensation expense in its statements of operations in the same manner in which the award recipient's payroll or service costs are classified.

Income Taxes

The Company accounts for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the consolidated financial statements or in the Company's tax returns. Under this method, deferred tax assets and liabilities are determined based on differences between the financial statement carrying amounts and the tax bases of the assets and liabilities using the enacted tax rates in effect in the years in which the differences are expected to reverse. A valuation allowance against deferred tax assets is recorded if, based on the weight of the available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized. Potential for recovery of deferred tax assets is evaluated by considering several factors, including estimating the future taxable profits expected, estimating future reversals of existing taxable temporary differences, considering taxable profits in carryback periods, and considering prudent and feasible tax planning strategies.

The Company accounts for uncertain tax positions using a more-likely-than-not threshold for recognizing and resolving uncertain tax positions. The evaluation of uncertain tax positions is based on factors including, but not limited to, changes in the law, the measurement of tax positions taken or expected to be taken in tax returns, the effective settlement of matters subject to audit, new audit activity, and changes in facts or circumstances related to a tax position.

Restructuring Expenses

The Company records costs and liabilities associated with exit and disposal activities in accordance with Accounting Standards Codification 420, *Exit or Disposal Cost Obligations*. Such costs are based on estimates of fair value in the period liabilities are incurred. The Company evaluates and adjusts these costs as appropriate for changes in circumstances as additional information becomes available.

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. For the years ended December 31, 2024 and 2023, comprehensive loss consists of net loss and unrealized gains on investments.

Net Income (Loss) Per Share

Basic net income (loss) per share is computed by dividing the net income (loss) by the weighted average number of shares of common stock outstanding for the period. Diluted net income (loss) per share is computed by dividing net income (loss) by the weighted average number of shares of common stock outstanding for the period, including potential dilutive common shares. For purpose of this calculation, outstanding options to purchase common stock and unvested restricted stock awards are considered potential dilutive common shares. The Company has generated a net loss in all periods presented, and therefore the basic and diluted net loss per share are the same as the inclusion of the potentially dilutive securities would be anti-dilutive.

Off-Balance Sheet Risk and Concentrations of Credit Risk

The Company has no significant off-balance sheet risk such as foreign exchange contracts, option contracts, or other foreign hedging arrangements. Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash, cash equivalents, marketable securities, and restricted cash. The Company's cash, cash equivalents, and restricted cash are deposited in accounts at large financial institutions. The Company believes it is not exposed to significant credit risk due to the financial strength of the depository institutions in which the cash, cash equivalents and restricted cash are held. The Company maintains its cash equivalents in money market funds that invest in U.S. Treasury

securities, and U.S. Treasury securities. The Company's marketable securities consist of U.S. Treasury securities, government agency securities, and corporate bonds, and potentially subject the Company to concentrations of credit risk. The Company has adopted an investment policy that limits the amounts the Company may invest in any one type of investment. The Company has not experienced any credit losses and does not believe it is exposed to any significant credit risk on these funds.

Segment Information

Operating segments are defined as components of an enterprise about which separate discrete financial information is available for evaluation by the chief operating decision-maker in making decisions regarding resource allocation and assessing performance. The Company and the Company's chief operating decision-maker, the Company's chief executive officer, view the Company's operations and manage its business as a single operating segment.

Recent Accounting Pronouncements—Adopted

In November 2023, the FASB issued ASU No. 2023-07, *Segment Reporting (Topic 280): Improvements to Reportable Segment Disclosures*. The standard updates reportable segment disclosure requirements, primarily through enhanced disclosures about significant segment expenses and information used to assess segment performance and requires companies to disclose all annual disclosures about segments in interim periods. The standard also requires companies with a single reportable segment to provide all disclosures required by Topic 280 – Segment Reporting. The new standard became effective for the Company on January 1, 2025. The adoption of this standard did not have a material impact on the Company's consolidated financial position and results of operations. See Note 16, "Segment Information", for further information regarding the adoption of this standard.

3. Fair Value Measurements

The following tables present information about the Company's financial assets measured at fair value on a recurring basis and indicate the fair value hierarchy classification of such fair values as of December 31, 2024 and 2023 (in thousands):

	Fair Value Measurements at December 31, 2024			
	Total	Level 1	Level 2	Level 3
Cash equivalents:				
Money market funds	$ 45,722	$ 45,722	$ —	$ —
U.S. Treasury securities	12,490	—	12,490	—
Marketable securities:				
U.S. Treasury securities	2,496	—	2,496	—
Government agency securities	11,282	—	11,282	—
Corporate bonds	169,031	—	169,031	—
Total	$ 241,021	$ 45,722	$ 195,299	$ —

	Fair Value Measurements at December 31, 2023			
	Total	Level 1	Level 2	Level 3
Cash equivalents:				
Money market funds	$ 25,563	$ 25,563	$ —	$ —
Marketable securities:				
U.S. Treasury securities	14,215	—	14,215	—
Government agency securities	65,107	—	65,107	—
Commercial paper	17,889	—	17,889	—
Corporate bonds	113,447	—	113,447	—
Total	$ 236,221	$ 25,563	$ 210,658	$ —

There were no transfers between fair value levels during the years ended December 31, 2024 and 2023.

4. Cash Equivalents and Marketable Securities

Cash equivalents and marketable securities consisted of the following as of December 31, 2024 and December 31, 2023 (in thousands):

	Fair Value Measurements at December 31, 2024			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Cash equivalents:				
Money market funds	$ 45,722	$ —	$ —	$ 45,722
U.S. Treasury securities	12,488	2	—	12,490
Total cash equivalents	58,210	2	—	58,212
Marketable securities:				
U.S. Treasury securities	2,496	—	—	2,496
Government agency securities	11,260	22	—	11,282
Corporate bonds	168,925	154	(48)	169,031
Total marketable securities	182,681	176	(48)	182,809
Total cash equivalents and marketable securities	$ 240,891	$ 178	$ (48)	$ 241,021

	Fair Value Measurements at December 31, 2023			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Cash equivalents:				
Money market funds	$ 25,563	$ —	$ —	$ 25,563
Total cash equivalents	25,563	—	—	25,563
Marketable securities:				
U.S. Treasury securities	14,229	10	(24)	14,215
Government agency securities	65,182	23	(98)	65,107
Commercial paper	17,891	8	(10)	17,889
Corporate bonds	113,492	90	(135)	113,447
Total marketable securities	210,794	131	(267)	210,658
Total cash equivalents and marketable securities	$ 236,357	$ 131	$ (267)	$ 236,221

There were no sales of marketable securities during the year ended December 31, 2024. As of December 31, 2024, the Company held 14 debt securities that were in an unrealized loss position for less than 12 months with an aggregate fair value of $40.0 million. As of December 31, 2024, the Company held no debt securities that were in an unrealized loss position for greater than 12 months. As of December 31, 2024, the aggregate fair value of marketable securities with a remaining contractual maturity of greater than one year was $5.8 million.

The Company has the intent and ability to hold its debt securities until recovery. As a result, the Company did not record any charges for credit-related impairments for its marketable securities for the year ended December 31, 2024.

5. Property and Equipment, Net

Property and equipment, net consisted of the following (in thousands):

	December 31, 2024	December 31, 2023
Lab equipment	$ 9,844	$ 9,682
Furniture and fixtures	600	600
Computer equipment	393	393
Software	199	199
Leasehold improvements	7,121	7,102
Total property and equipment	18,157	17,976
Less: accumulated depreciation	(14,257)	(12,760)
Property and equipment, net	$ 3,900	$ 5,216

Depreciation expense for the years ended December 31, 2024 and 2023 was $1.6 million and $2.2 million, respectively.

6. Additional Balance Sheet Detail

Prepaid expenses and other current assets consisted of the following (in thousands):

	December 31, 2024	December 31, 2023
Prepaid expenses	$ 5,560	$ 3,658
Prepaid sign-on bonuses subject to vesting provisions	—	71
Interest income receivable	1,246	1,712
Total prepaid expenses and other current assets	$ 6,806	$ 5,441

Accrued expenses and other current liabilities consisted of the following (in thousands):

	December 31, 2024	December 31, 2023
External research and development	$ 3,561	$ 3,164
Payroll and benefits	2,988	4,712
Professional services	682	454
Other	463	396
Total accrued expenses and other current liabilities	$ 7,694	$ 8,726

7. Preferred Stock

As of December 31, 2024 and 2023, 5,000,000 shares of undesignated preferred stock were authorized. No shares of preferred stock were issued or outstanding as of December 31, 2024 and 2023.

No dividends have been declared since inception.

8. Common Stock

As of December 31, 2024 and 2023, 200,000,000 shares of common stock, $0.001 par value per share, were authorized.

Each share of common stock entitles the holder to one vote on all matters submitted to a vote of the Company's stockholders. Common stockholders are not entitled to receive dividends, unless declared by the Company's board of directors, subject to the preferential dividend rights of any preferred stock then outstanding. No dividends have been declared or paid by the Company since its inception.

As of December 31, 2024 and 2023, the Company has reserved for future issuance the following number of shares of common stock:

	December 31, 2024	December 31, 2023
Shares reserved for exercises of outstanding stock options	9,354,699	9,972,217
Shares reserved for vesting of restricted stock units	43,072	75,017
Shares reserved for future issuance under the 2019 Stock Incentive Plan	5,207,362	3,157,537
Shares reserved for future issuance under the 2019 Employee Stock Purchase Plan	1,671,843	1,346,125
Shares reserved for future issuance under the 2022 Inducement Stock Incentive Plan	1,896,209	837,877
Shares reserved for future issuance for pre-funded warrants	8,500,000	—
	26,673,185	15,388,773

Pre-Funded Warrants

In August 2024, the Company entered into separate exchange agreements with RA Capital Healthcare Fund, L.P. ("RA Capital") and another existing institutional stockholder, pursuant to which (i) RA Capital exchanged 8,500,000 shares of the Company's common stock for a pre-funded warrant to acquire 8,500,000 shares of the Company's common stock and (ii) the other existing institutional stockholder exchanged an aggregate of 850,000 shares of the Company's common stock, for pre-funded warrants to acquire an aggregate of 850,000 shares of the Company's common stock. The aggregate 9,350,000 shares of common stock subject to the exchange agreements were retired on the date of the exchanges. As of December 31, 2024, 850,000 pre-funded warrants have been exercised.

The pre-funded warrants have an exercise price of $0.001 per underlying share of common stock, are immediately exercisable and have no expiration date. The number of shares of the Company's common stock issuable upon exercise of each pre-funded warrant is subject to adjustment upon certain corporate events, including certain stock dividends and splits, combinations, reclassifications, and certain other events. The pre-funded warrants include a beneficial ownership blocker that provides that the holder may not exercise (nor may we allow the exercise) if upon giving effect to such exercise, it would cause the aggregate number of shares of the Company's common stock beneficially owned by the holder (together with affiliates and any other persons whose beneficial ownership of the Company's common stock would be aggregated for the purposes of Section 13(d) of the Securities Exchange Act of 1934, as amended) to exceed 9.99% of the total number of then issued and outstanding shares of the Company's common stock as determined in accordance with the terms of the pre-funded warrant. This threshold may be increased or decreased upon 61 days' prior notice at the discretion of RA Capital, but not in excess of 19.99% or, with respect to the other existing institutional stockholder's pre-funded warrants, not in excess of 9.99%.

The Company assessed the pre-funded warrants for appropriate classification as either equity or liability pursuant to the Company's accounting policy described in Note 2, "Summary of Significant Accounting Policies." The Company determined the pre-funded warrants are freestanding instruments that do not meet the definition of a liability pursuant to ASC 480 and do not meet the definition of a derivative pursuant to ASC 815. The pre-funded warrants are indexed to the Company's common stock and meet all other conditions for equity classification under ASC 480 and ASC 815. Accordingly, the pre-funded warrants are classified as equity and are accounted for as a component of additional paid-in capital at the time of issuance. The Company also determined that the pre-funded warrants should be included in the determination of basic and diluted earnings per share.

9. Stock-based Compensation Expense

2016 Stock Incentive Plan

In July 2016, the Company adopted the 2016 Stock Incentive Plan (the "2016 Plan"), which provided for the grant of restricted stock awards, restricted stock units, incentive stock options, non-statutory stock options, and other stock-based awards to the Company's eligible employees, officers, directors, consultants, and advisors. As of the effective date of the 2019 Stock Incentive Plan (the "2019 Plan"), and as of December 31, 2024 and 2023, no shares remained available for future issuance under the 2016 Plan. Any options or other awards outstanding under the 2016 Plan remain outstanding and effective.

2019 Stock Incentive Plan

On July 2, 2019, the Company's stockholders approved the 2019 Plan, which became effective on July 17, 2019. The 2019 Plan provides for the grant of incentive stock options, non-statutory stock options, stock appreciation rights, restricted stock awards, restricted stock units and other stock-based awards to the Company's officers, employees, directors, consultants and advisors. The number of shares initially reserved for issuance under the 2019 Plan was 2,017,142 shares, plus the shares of common stock remaining available for issuance under the 2016 Plan as of July 17, 2019. The number of shares reserved was increased on January 1, 2020 and will be increased each January 1 thereafter through January 1, 2029 by the least of (i) 2,000,000 shares, (ii) 4% of the number of shares of the Company's common stock outstanding on the first day of each such year or (iii) an amount determined by the Company's board of directors. As of December 31, 2024, there were 5,207,362 shares available for future issuance under the 2019 Plan. On January 1, 2025, the number of shares reserved for issuance under the 2019 Plan was increased by 2,000,000 shares.

The shares of common stock underlying any awards that expire, terminate, or are otherwise surrendered, cancelled, forfeited or repurchased by the Company under the 2016 Plan or the 2019 Plan will be added back to the shares of common stock available for issuance under the 2019 Plan. As of July 17, 2019, no further awards will be made under the 2016 Plan.

2022 Inducement Stock Incentive Plan

In February 2022, the Company's board of directors adopted the 2022 Inducement Stock Incentive Plan (the "Inducement Plan"), pursuant to which the Company may grant, subject to the terms of the Inducement Plan and Nasdaq rules, nonstatutory stock options, stock appreciation rights, restricted stock awards, restricted stock units, and other stock-based awards. The Company initially reserved a total of 1,750,000 shares of common stock for the issuance of awards under the Inducement Plan. The number of shares reserved and available for issuance under the Inducement Plan can be increased at any time with the approval of the Company's board of directors. The Inducement Plan permits the board of directors, a delegated committee of the board of directors, or a delegated officer of the Company to grant the stock-based awards available under the Inducement Plan to attract key employees for the growth of the Company. Effective March 8, 2023, the Company's board of directors amended the Inducement Plan to increase the number of shares reserved for issuance by 2,000,000 shares. Effective May 18, 2023, the Company's board of directors amended the Inducement Plan to increase the number of shares reserved for issuance by 1,400,000 shares. Effective June 17, 2024, the Company's board of directors amended the Inducement Plan to increase the number of shares reserved for issuance by 1,000,000 shares. As of December 31, 2024, there were 1,896,209 shares available for future issuance under the Inducement Plan.

Stock Options

Stock options granted by the Company typically vest over a four year period and have a ten year contractual term. Shares issued upon the exercise of stock options are issued from the Company's pool of authorized but unissued common stock. In addition to stock options granted under the 2019 Plan and 2016 Plan, the Company has granted stock options as material inducements to employment in accordance with Nasdaq Listing Rule 5635(c)(4), which were granted outside of the 2019 Plan and 2016 Plan. The following table summarizes the Company's stock option activity during the year ended December 31, 2024:

	Number of Shares	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in years)	Aggregate Intrinsic Value
Outstanding at December 31, 2023	9,972,217	$ 8.44	8.49	$ 15,114,074
Granted	4,226,008	7.70		
Exercised	(427,757)	5.62		
Cancelled	(4,415,769)	10.08		
Outstanding at December 31, 2024	9,354,699	$ 7.46	8.03	$ 5,353,463
Exercisable at December 31, 2024	4,349,742	$ 9.06	7.35	$ 2,045,339

The aggregate intrinsic value of stock options is calculated as the difference between the exercise price of the stock options and the fair value of the Company's common stock as of the balance sheet date for those options that had exercise prices lower than the fair value of the Company's common stock.

The weighted average grant date fair value of stock options granted in the years ended December 31, 2024 and 2023 was $6.31 per share and $4.64 per share, respectively. The total intrinsic value of stock options exercised in the years ended December 31, 2024 and 2023 was $1.4 million and $0.2 million, respectively.

The fair value of stock options granted during the years ended December 31, 2024 and 2023 has been calculated on the date of grant using the following weighted average assumptions:

	Year Ended December 31, 2024	Year Ended December 31, 2023
Risk-free interest rate	4.1%	3.7%
Expected dividend yield	0.0%	0.0%
Expected term (years)	6.0	6.1
Expected stock price volatility	103.3%	98.6%

Restricted Stock Units

The Company has also granted restricted stock units. The shares of common stock underlying restricted stock units typically vest over a four-year period. The shares of common stock are recorded in stockholders' equity as they vest.

The following table summarizes the Company's restricted stock unit activity during the year ended December 31, 2024:

	Number of Shares	Weighted Average Grant Date Fair Value
Unvested at December 31, 2023	75,017	$ 10.77
Granted	70,445	6.95
Vested	(22,326)	10.65
Cancelled	(80,064)	8.26
Unvested at December 31, 2024	43,072	$ 9.25

The aggregate intrinsic value of all restricted stock units and restricted stock awards that vested during the years ended December 31, 2024 and 2023 was $0.2 million and $0.1 million, respectively.

Stock-based Compensation Expense

The total compensation cost recognized in the statements of operations and comprehensive loss associated with all stock-based compensation awards granted by the Company is as follows (in thousands):

	Year Ended December 31, 2024	2023
General and administrative	$ 9,901	$ 11,026
Research and development	4,653	3,776
Total stock-based compensation expense	$ 14,554	$ 14,802

As of December 31, 2024, the Company had an aggregate of $21.6 million of unrecognized stock-based compensation expense, which is expected to be recognized over a weighted average period of 2.4 years.

2019 Employee Stock Purchase Plan

On July 2, 2019, the Company's stockholders approved the 2019 Employee Stock Purchase Plan (the "ESPP"), which became effective on July 17, 2019. A total of 252,142 shares of common stock were initially reserved for issuance under the ESPP. In addition, the number of shares of common stock reserved under the ESPP was increased on January 1, 2020, and will be increased annually on each January 1 thereafter through January 1, 2029, by the least of (i) 428,571 shares of common

stock, (ii) 1% of the number of shares of the Company's common stock outstanding on the first day of each such year or (iii) an amount determined by the Company's board of directors. As of December 31, 2024, there were 1,671,843 shares available for future issuance under the ESPP. On January 1, 2025, the number of shares reserved for issuance under the 2019 ESPP was increased by 428,571 shares.

10. License and Collaboration Agreements

Sanofi Agreement

In May 2024, the Company entered into a collaboration and license agreement (the "Sanofi Agreement") with Genzyme Corporation ("Sanofi") pursuant to which the Company granted Sanofi an exclusive license under certain intellectual property rights to commercialize losmapimod, an oral small molecule for the treatment of facioscapulohumeral muscular dystrophy ("FSHD"), outside of the United States. On December 18, 2024, the Company received written notice of Sanofi's election to terminate for convenience the collaboration and license agreement. In accordance with the agreement, the termination will become effective on April 17, 2025, which is 120 days following the date of receipt of the notice by the Company.

Until the termination of the agreement, the parties will continue to perform their respective obligations under the agreement. As of the termination date, the agreement will be terminated in its entirety, following which the Company will not be entitled to receive any further milestone payments, royalties, or global development cost reimbursement.

Under the agreement, pursuant to a mutually agreed global development plan, the Company continued the Phase 3 clinical trial for losmapimod for the treatment of FSHD, and the Company and Sanofi agreed to equally share global development costs. In addition to potential future activities conducted under a mutually agreed global development plan, Sanofi had the right to conduct certain development activities that were solely intended to support obtaining or maintaining regulatory approval outside of the United States. The Company had the sole right to manufacture for its activities under the global development plan and for commercialization in the United States and, subject to the terms of a supply agreement, the Company was to have supplied Sanofi's clinical and commercial supply requirements of losmapimod until Sanofi elected to take over such manufacturing responsibilities.

Per the terms of the agreement, Sanofi made an upfront payment of $80.0 million to the Company. The Company was also eligible to receive up to an additional $975.0 million in specified regulatory and sales-based milestones, and Sanofi agreed to pay the Company tiered royalties ranging from low-teens to mid-twenties based on Sanofi's and any of its affiliates' and sublicensees' annual net sales of losmapimod outside the United States. The royalties were payable on a product-by-product basis during a specified royalty term, and could have been reduced in specified circumstances.

During the term of the Sanofi Agreement, the Company may not research, develop, manufacture, commercialize, use, or otherwise exploit any compound or product that binds or otherwise modulates p38a/b MAPK anywhere in the world, other than losmapimod in the United States.

The Sanofi Agreement was to continue on a country-by-country and product-by-product basis until the last to expire royalty term for a product in a country, at which time the Sanofi Agreement expires with respect to such product in such country. Either party had the right to terminate the Sanofi Agreement if the other party had materially breached its obligations under the Sanofi Agreement and such breach had not been cured within the applicable cure period. Sanofi also had the right to terminate the Sanofi Agreement for convenience in its entirety, which it exercised on December 18, 2024. The Company had the right to terminate the Sanofi Agreement if Sanofi terminated all bona fide material development and commercialization activities for a specified period and such cessation is not the result of certain agreed upon reasons.

The Company determined that the Sanofi Agreement contained three material promises: (i) the license granted to Sanofi to develop and commercialize losmapimod outside of the United States (the "losmapimod license"); (ii) the parties' joint global development activities for losmapimod; and (iii) the Sanofi territory-specific manufacturing activities for losmapimod, subject to the terms of a supply agreement. The Company considered the guidance in ASC 606 to determine which, if any, of the components of the losmapimod agreement are performance obligations with a customer and concluded that the losmapimod license and the Sanofi territory-specific manufacturing activities are within the scope of ASC 606 because Sanofi is the Company's customer in those transactions.

The Company evaluated the losmapimod license under ASC 606 and concluded that the losmapimod license is a functional intellectual property license and is a distinct performance obligation. The Company determined that Sanofi benefited from the losmapimod license at the time of grant, and therefore the related performance obligation is satisfied at a point in time.

The Company evaluated the Sanofi territory-specific manufacturing activities under ASC 606 and identified one material promise associated with manufacturing activities related to development and commercial supply of losmapimod. Given that Sanofi is not obligated to purchase any minimum amount or quantities of the development and commercial supply from the Company, the Company concluded that, for the purpose of ASC 606, the provision of manufacturing activities related to development and commercial supply of losmapimod in the Sanofi territory was an option but not a performance obligation of the Company at the inception of the Sanofi agreement and would be accounted for if and when exercised. The Company also concluded that there is no separate material right in connection with the development and commercial supply of losmapimod, as the expected pricing was not issued at a significant and incremental discount. Therefore, the manufacturing activities were excluded as a performance obligation at the outset of the arrangement. Additionally, the Company was entitled to sales milestones and royalties from Sanofi upon future sales of losmapimod in the Sanofi territory, and revenue would have been recognized when the related sales occur. Costs that are incurred associated with the Sanofi territory-specific manufacturing activities are reimbursable from Sanofi and will be recognized as revenue.

For the purposes of ASC 606, the transaction price of the Sanofi Agreement as of the outset of the arrangement consists of the upfront cash payment of $80.0 million, which was allocated to the performance obligation related to the losmapimod license. The other potential milestone payments that the Company is eligible to receive under the Sanofi agreement have been excluded from the transaction price, as all the remaining milestone amounts were fully constrained based on the probability of achievement. During the year ended December 31, 2024, the Company recognized $80.0 million of revenue associated with the upfront license payment.

For the parties' participation in global development for losmapimod, the Company concluded that those activities and cost-sharing payments related to such activities are within the scope of ASC 808, as both parties are active participants in the development activities and are exposed to significant risks and rewards of those activities under the Sanofi agreement. The Company assessed its relationship with Sanofi, the economics and nature of the global development activities, and the contractual terms of the Sanofi Agreement and concluded that, in accordance with its policy, payments to or reimbursements from Sanofi related to the global development activities will be accounted for as an increase to or reduction of research and development expenses. During the year ended December 31, 2024, the Company recorded a reduction in research and development expenses in connection with global development activities for losmapimod of $8.1 million.

GSK Agreement

In February 2019, the Company entered into the right of reference and license agreement, as amended (the "GSK Agreement"), with subsidiaries of GlaxoSmithKline plc (collectively referred to as "GSK"), pursuant to which the Company has been granted an exclusive worldwide license to develop and commercialize losmapimod. Under the GSK Agreement, the Company also acquired reference rights to relevant regulatory and manufacturing documents and GSK's existing supply of losmapimod drug substance and product. The Company also has the right to sublicense its rights under the license agreement, subject to certain conditions. The Company is obligated to use commercially reasonable efforts to develop and commercialize losmapimod at its sole cost. The Company is also responsible for costs related to the filing and maintenance of the licensed patent rights.

Under the GSK Agreement, the Company issued 12,500,000 shares of Series B Preferred Stock to GSK (all of which converted to common stock in connection with the Company's 2019 initial public offering). In addition, the Company may owe GSK up to $37.5 million in certain specified clinical and regulatory milestones, including a $5.0 million milestone that was achieved during 2022 and a $2.5 million milestone that was achieved 2019, and up to $60.0 million in certain specified sales milestones. The Company agreed to pay tiered royalties on annual net sales of losmapimod that range from mid single-digit percentages to a low double-digit, but less than teens, percentage. The royalties are payable on a product-by-product and country-by-country basis, and may be reduced in specified circumstances.

The GSK Agreement may be terminated by either party for a material breach by the other, subject to notice and cure provisions. Unless earlier terminated, the GSK Agreement will continue in effect until the expiration of the Company's royalty obligations, which expire on a country-by-country basis on the later of (i) ten years after the first commercial sale in the country or (ii) approval of a generic version of losmapimod by the applicable regulatory agency.

The Company recognizes clinical and regulatory milestone payments when the underlying contingency is resolved and the consideration is paid or becomes payable. The milestone payments are capitalized or expensed depending on the nature of the associated asset as of the date of recognition.

MyoKardia Agreement

On July 20, 2020, the Company entered into the MyoKardia Collaboration Agreement, pursuant to which the Company granted to MyoKardia an exclusive worldwide license under certain intellectual property rights to research, develop, make, have made, use, have used, sell, have sold, offer for sale, have offered for sale, import, have imported, export, have exported, distribute, have distributed, market, have marketed, promote, have promoted, or otherwise exploit products directed against certain biological targets identified by the Company that are capable of modulating up to a certain number of genes of interest with relevance to certain genetically defined cardiomyopathies.

Pursuant to a mutually agreed research plan, the Company performed assay screening and related research activities to identify and validate up to a specified number of potential cardiomyopathy gene targets ("Identified Targets") for further research, development, manufacture and commercialization by MyoKardia. The Company and MyoKardia worked together to determine how best to advance at each stage of the research activities under the research plan and to identify which of the Identified Targets, if any, met the criteria set forth in the research plan (the "Cardiomyopathy Target Candidates"). Upon completion of the research plan, the parties will work together to prepare a final data package and MyoKardia may designate certain Cardiomyopathy Target Candidates for MyoKardia's further exploitation under the MyoKardia Collaboration Agreement (the "Cardiomyopathy Targets"). If MyoKardia does not designate any Cardiomyopathy Targets during the designated period, then the MyoKardia Collaboration Agreement will automatically terminate. If MyoKardia designates one or more Cardiomyopathy Targets, then MyoKardia will be obligated to use commercially reasonable efforts to seek regulatory approval for and to commercialize one product directed against an Identified Target in certain specified countries.

During the period in which the Company performed the research activities pursuant to the research plan (the "Research Term") and for a specified period beyond the Research Term if MyoKardia designates a Cardiomyopathy Target, the Company may only use the data generated from such research activities for MyoKardia in accordance with the MyoKardia Collaboration Agreement. During the Research Term and for a specified period thereafter, the Company may not research, develop, manufacture, commercialize, use, or otherwise exploit any compound or product (a) that is a Compound or Product under the MyoKardia Collaboration Agreement that is directed against the Cardiomyopathy Target Candidates for the treatment, prophylaxis, or diagnosis of any indication or (b) for the treatment of any genetically defined cardiomyopathies shown to be related to certain specified genes of interest that are modulated by the Cardiomyopathy Targets.

Under the MyoKardia Collaboration Agreement, MyoKardia made a $10.0 million upfront payment and a $2.5 million payment as prepaid research funding to the Company in July 2020. MyoKardia also reimbursed the Company for the costs of the research activities not covered by the prepaid research funding, up to a maximum amount of total research funding (including the prepaid research funding). Upon the achievement of specified preclinical, development and sales milestones, the Company will be entitled to preclinical milestone payments, development milestone payments and sales milestone payments of up to $298.5 million in the aggregate per target for certain Identified Targets, and of up to $150.0 million in the aggregate per target for certain other Identified Targets. To date, the Company has achieved a $2.5 million specified preclinical milestone. MyoKardia will also pay the Company tiered royalties ranging from a mid single-digit percentage to a low double-digit percentage based on MyoKardia's, and any of its affiliates' and sublicensees', annual worldwide net sales of products under the MyoKardia Collaboration Agreement directed against any Identified Target. The royalties are payable on a product-by-product basis during a specified royalty term, and may be reduced in specified circumstances.

The MyoKardia Collaboration Agreement continues on a country-by-country and product-by-product basis until the last to expire royalty term for a product, at which time the MyoKardia Collaboration Agreement expires with respect to such product in such country. Either party has the right to terminate the MyoKardia Collaboration Agreement if the other party has materially breached in the performance of its obligations under the MyoKardia Collaboration Agreement and such breach has not been cured within the applicable cure period. MyoKardia also has the right to terminate the MyoKardia Collaboration Agreement for convenience in its entirety or on a target-by-target, product-by-product or molecule-by-molecule basis.

In July 2024, the Company entered into an amendment to the MyoKardia Collaboration Agreement, pursuant to which the Company and MyoKardia agreed to extend the Research Term.

Accounting Analysis

Identification of the Contract

The Company assessed the MyoKardia Collaboration Agreement and concluded that it represents a contract with a customer within the scope of ASC 606.

Identification of the Promises and Performance Obligations

The Company determined that the MyoKardia Collaboration Agreement contains the following promises: (i) an exclusive worldwide license under certain intellectual property rights, including rights to a specified number of potential cardiomyopathy gene targets identified by the Company for further research, development, manufacture and commercialization for the treatment, prophylaxis, or diagnosis of certain genetically defined cardiomyopathies that was conveyed at the inception of the arrangement (the "MyoKardia License"), (ii) research services to identify and validate potential biological targets (the "MyoKardia Research Services"), and (iii) participation in the joint steering committee (the "MyoKardia JSC").

The Company assessed the above promises and concluded that the MyoKardia License is not capable of being distinct from the MyoKardia Research Services given that the MyoKardia License has limited value without the performance of the MyoKardia Research Services and the MyoKardia Research Services can only be performed by the Company due to their specialized nature. Therefore, the Company has concluded that the MyoKardia License and the MyoKardia Research Services represent a single combined performance obligation.

The Company also assessed the participation on the MyoKardia JSC and concluded that the promise is quantitatively and qualitatively immaterial in the context of the MyoKardia Collaboration Agreement. Accordingly, the Company has disregarded its participation on the MyoKardia JSC as a performance obligation.

Determination of the Transaction Price

The Company received a non-refundable upfront payment of $10.0 million, which the Company included in the transaction price. In December 2021, the Company achieved a $2.5 million specified preclinical milestone associated with the MyoKardia Collaboration Agreement, which was previously constrained due to the significant uncertainty regarding whether such preclinical milestone would be achieved. The Company included this amount in the transaction price as of December 31, 2021. Based on the continued uncertainty associated with the achievement of any of the remaining preclinical and development milestone payments that the Company is eligible to receive, the Company has constrained the variable consideration associated with those milestone payments and excluded them from the transaction price. As part of its evaluation of constraining the preclinical and development milestones, the Company considered numerous factors, including the fact that the achievement of the preclinical and development milestones are contingent upon the results of the underlying preclinical and development activities and are thus outside of the control of the Company.

The Company also included in the transaction price the expected amount of costs to be reimbursed for the MyoKardia Research Services, which includes the $2.5 million prepaid research funding payment that the Company received in the third quarter of 2020.

The Company reassesses the transaction price at the end of each reporting period and as uncertain events are resolved or other changes in circumstances occur, and, if necessary, adjusts its estimate of the transaction price. There was no change in the amount of variable consideration constrained during the year ended December 31, 2024.

Any consideration related to sales milestone payments (including royalties) will be recognized when the related sales occur as these amounts have been determined to relate predominantly to the license granted to MyoKardia and therefore are recognized at the later of when the related sales occur or the performance obligation is satisfied.

Allocation of the Transaction Price to Performance Obligations

As noted above, the Company has identified a single performance obligation associated with the MyoKardia Collaboration Agreement. Therefore, the Company will allocate the entire amount of the transaction price to the identified single performance obligation.

Recognition of Revenue

The Company recognizes revenue related to the MyoKardia Collaboration Agreement over time as the MyoKardia Research Services are rendered. The Company has concluded that an input method is a representative depiction of the transfer of services under the MyoKardia Collaboration Agreement. The method of measuring progress towards the delivery of the services incorporates actual cumulative internal and external costs incurred relative to total internal and external costs expected to be incurred to satisfy the performance obligation. The period over which total costs are estimated reflects the Company's estimate of the period over which it will perform the MyoKardia Research Services. Changes in estimates of total internal and external costs expected to be incurred are recognized in the period of change as a cumulative catch-up adjustment. The Company satisfied its obligation to perform research services as of December 31, 2023.

During the year ended December 31, 2024, the Company recognized no collaboration revenue associated with the MyoKardia Collaboration Agreement. During the year ended December 31, 2023, the Company recognized $2.8 million of collaboration revenue associated with the MyoKardia Collaboration Agreement, which includes $0.9 million of revenue recognized that was included in deferred revenue as of December 31, 2022. As of December 31, 2024 and December 31, 2023, the Company recorded no deferred revenue associated with the MyoKardia Collaboration Agreement. As of December 31, 2024, the Company had received $7.7 million of cost reimbursement payments under the MyoKardia Collaboration Agreement and $2.5 million associated with the achievement of a preclinical milestone, respectively. As of December 31, 2023, the Company had received $7.2 million of cost reimbursement payments under the MyoKardia Collaboration Agreement and $2.5 million associated with the achievement of a preclinical milestone, respectively. As of December 31, 2024, the Company recorded no unbilled accounts receivable related to reimbursable research and development costs under the MyoKardia Collaboration Agreement for activities performed during the three months ended December 31, 2024. As of December 31, 2023, the Company recorded unbilled accounts receivable of $0.5 million related to reimbursable research and development costs under the MyoKardia Collaboration Agreement for activities performed during the three months ended December 31, 2023. As of December 31, 2024 and 2023, the Company recorded no accounts receivable under the MyoKardia Collaboration Agreement.

CAMP4 Agreement

In July 2023, the Company entered into a license agreement (the "CAMP4 Agreement") with CAMP4 Therapeutics Corporation ("CAMP4") pursuant to which the Company received a worldwide exclusive license (including the right to sublicense) from CAMP4 to rights under its Diamond Blackfan Anemia ("DBA") program, which includes certain small molecule compounds, composition of matter and method of use patent rights, and know-how for the Company to research, develop, manufacture, use, commercialize or otherwise exploit therapeutic products in any indication, including the grant of a sublicense under certain intellectual property rights that CAMP4 has licensed under an agreement with Children's Medical Center Corporation ("CMCC").

The Company made an undisclosed upfront non-refundable, non-creditable payment to CAMP4. If the Company succeeds in developing and commercializing licensed products, CAMP4 will be eligible to receive (i) up to $35.0 million in development and regulatory milestone payments, and (ii) up to $35.0 million in sales milestone payments. CAMP4 is also eligible to receive royalties on worldwide net sales of licensed products ranging from mid-single digit to low-double digit, subject to potential reduction following loss of patent coverage, the launch of certain generic products or royalty stacking for licenses of third party intellectual property. The royalties will expire on a product-by-product and country-by-country basis upon the latest to occur of (i) the expiration of all valid patent claims covering the compounds in such country, (ii) the expiration of all regulatory exclusivities in such country, and (iii) 10 years following the first commercial sale in such country. The Company is responsible for the costs associated with the development and regulatory approvals of licensed products.

Unless earlier terminated in accordance with its terms, the license agreement continues on a country-by-country and licensed product-by-licensed product basis until the expiration of the royalty term in each country, at which time the license agreement expires with respect to such licensed product in such country and the Company will have a fully-paid up, royalty-free and perpetual license to the licensed patent rights and know-how with respect to such licensed product in such country. CAMP4 has the right to terminate the license agreement in the event of the Company's non-payment (subject to cure periods and tolling for bona fide disputes). CAMP4 may also terminate the license agreement if the Company challenges certain patents sublicensed to the Company by CAMP4. Either party may terminate the license agreement in its entirety for the other party's material breach if such other party fails to cure the breach. Either party may also terminate the agreement in its entirety upon certain insolvency events involving the other party. The Company has the right to terminate the license agreement with CAMP4 for any or no reason upon prior written notice to CAMP4.

The Company recognizes development and regulatory milestone payments when the underlying contingency is resolved and the consideration is paid or becomes payable. The milestone payments are capitalized or expensed depending on the nature of the associated asset as of the date of recognition.

11. Leases

Operating Leases

26 Landsdowne Street

In November 2017, the Company entered into a lease agreement for its current corporate headquarters comprising approximately 28,731 square feet of office and laboratory space at 26 Landsdowne Street in Cambridge, Massachusetts, commencing December 2017. The Company began to occupy and use the leased space for its intended purpose in June 2018.

The lease ends on June 30, 2028. The Company has the option to extend the term of the lease for an additional five-year period, at the market rate, by giving the landlord written notice of its election to exercise the extension at least nine months prior to the original expiration of the lease term. The lease has a total commitment of $25.1 million over the ten year term, and includes escalating rent payments. The lease provides the Company with an allowance for normal leasehold improvements of $5.0 million. The lease agreement requires the Company to either pay a security deposit or maintain a letter of credit of $1.1 million. The Company maintains a letter of credit for this lease and has recorded the cash held to secure the letter of credit as restricted cash on the consolidated balance sheet as of December 31, 2024 and December 31, 2023. Operating lease and variable lease expense associated with this lease for the years ended December 31, 2024 and 2023 was approximately $1.9 million and $0.9 million, respectively.

The future minimum lease payments associated with the 26 Landsdowne Street lease as of December 31, 2024, are as follows (in thousands):

2025		2,649
2026		2,729
2027		2,811
Thereafter		1,426
Total minimum lease payments		9,615
Less: imputed interest		(986)
Total lease liability	$	8,629

125 Sidney Street

In November 2021, the Company entered into a lease agreement comprising approximately 12,196 square feet of office space at 125 Sidney Street in Cambridge, Massachusetts, commencing November 2021. The Company began recognizing rent expense associated with this lease during November 2021. The lease ended on March 31, 2024. The Company had the option to extend the term of the lease for two successive one-year periods, at the market rate, by giving the landlord written notice of its election to exercise the extension at least nine months prior to the original expiration of the lease term. The lease had a total commitment of $1.7 million over the initial term, and included escalating rent payments. Operating lease expense associated with this lease for the year ended December 31, 2024 was approximately $0.2 million. No variable lease expense was recorded associated with this lease for the year ended December 31, 2024.

There are no future minimum lease payments associated with this lease as of December 31, 2024.

12. Commitments and Contingencies

Indemnification Agreements

In the ordinary course of business, the Company may provide indemnification of varying scope and terms to vendors, lessors, business partners and other parties with respect to certain matters arising out of the relationship between such parties and the Company. In addition, the Company has entered into indemnification agreements with members of its board of directors and senior management that will require the Company, among other things, to indemnify them against certain liabilities that may arise by reason of their status or service as directors or officers. The maximum potential amount of future payments the Company could be required to make under these indemnification agreements is, in many cases, unlimited. To date, the Company has not incurred any material costs as a result of such indemnifications. The Company is not aware of any claims under indemnification arrangements, and it has not accrued any liabilities related to such obligations as of December 31, 2024 or 2023.

Legal Proceedings

On April 28, 2023, a class action complaint was filed in the United States District Court for the District of New Jersey against the Company and current and former officers (the "Securities Action"). On May 19, 2023, the Securities Action was transferred to the United States District Court for the District of Massachusetts, captioned Celano v. Fulcrum Therapeutics, Inc., et al., Case No. 1:23-cv-11125-IT. On July 31, 2023, the court appointed a lead plaintiff, who filed an amended complaint on September 29, 2023. The Securities Action alleges violations of Section 10(b) of the Securities Exchange Act of 1934, as amended, and Rule 10b-5 promulgated thereunder against all defendants and control person violations of Section 20(a) against the individuals, related to the Company's February 2023 announcement that the U.S. Food and Drug Administration issued a clinical hold regarding the investigational new drug application for pociredir for the potential treatment of sickle cell disease. The Securities Action alleges that the defendants made misleading statements and omitted to disclose material information related to the clinical hold and seeks, among other things, compensatory damages in connection

with an allegedly inflated stock price between March 3, 2022, and March 8, 2023, as well as attorneys' fees and costs. On November 28, 2023, all defendants filed a motion to dismiss the Securities Action. Briefing was completed on the motion in February 2024, and the court held a hearing on the motion in September 2024. The Company intends to defend vigorously against this litigation.

At each reporting date, the Company evaluates whether or not a potential loss amount or a potential range of loss is probable and reasonably estimable under the provisions of the authoritative guidance that addresses accounting for contingencies. The Company expenses the costs related to its legal proceedings as they are incurred. Other than attorneys' fees and costs related to the defense of the Securities Action, no such costs have been incurred during the year ended December 31, 2024.

13. Income Taxes

A reconciliation of the U.S. federal statutory income tax rate to the Company's effective income tax rate is as follows:

	Year Ended December 31, 2024	Year Ended December 31, 2023
Federal income tax at statutory rate	21.00%	21.00%
Permanent differences	(0.90)	(0.04)
Federal and state research and development credits	15.14	1.47
Federal orphan drug credits	77.47	9.41
State income tax, net of federal benefit	6.09	5.92
Stock compensation (incentive stock options)	(6.23)	(0.68)
Stock compensation cancellations	(17.71)	(0.18)
Officers' compensation	(5.11)	(1.06)
Impact of ownership change	(1,283.66)	—
Deferred rate change	(6.78)	(0.02)
Other	3.75	0.11
Change in valuation allowance	1,196.94	(35.93)
Effective income tax rate	—%	—%

During the years ended December 31, 2024 and 2023, the Company incurred book and tax losses and, because it maintains a full valuation allowance on its net deferred tax assets, did not recognize federal or state income tax expense or benefit.

The Company's deferred tax assets and liabilities consist of the following (in thousands):

	December 31, 2024	December 31, 2023
Deferred tax assets:		
Capitalized research and development costs	$ 38,850	$ 30,019
Net operating loss carryforwards	1,436	85,622
Orphan drug credit carryforwards	2,193	23,790
Research and development credit carryforwards	422	11,569
Intangible assets	2,705	6,291
Accrued expenses and other	6,760	6,740
Operating lease liability	2,287	2,911
Gross deferred tax assets	54,653	166,942
Valuation allowance	(51,753)	(164,483)
Net deferred tax assets	2,900	2,459
Deferred tax liability	(2,900)	(2,459)
Net deferred tax assets	$ —	$ —

The Company has evaluated the positive and negative evidence bearing upon its ability to realize the net deferred tax assets. The Company considered its history of cumulative net losses incurred since inception and its lack of commercialization of any products since inception and has concluded that it is more likely than not that the Company will not

realize the benefits of the net deferred tax assets. Accordingly, a full valuation allowance has been established against the net deferred tax assets as of December 31, 2024 and 2023. The valuation allowance decreased by $112.7 million during the year ended December 31, 2024, which is primarily attributable to a limitation under Section 382 of the Internal Revenue Code of 1986, as amended (the "Internal Revenue Code"), related to the Company's net operating loss carryforwards and research and development tax credit carryforwards, as discussed further below. The Company reevaluates the positive and negative evidence at each reporting period.

As of December 31, 2024, the Company had federal net operating loss carryforwards of approximately $5.0 million, which may be available to offset future taxable income and do not expire, but are limited in their usage to an annual deduction equal to 80% of annual taxable income. As of December 31, 2024, the Company also had state net operating loss carryforwards of approximately $6.2 million, which begin to expire in 2044.

As of December 31, 2024, the Company had federal orphan drug credits of approximately $2.2 million, which begin to expire in 2044. As of December 31, 2024, the Company had federal research and development tax credit carryforwards of approximately $0.3 million, which begin to expire in 2039. As of December 31, 2024, the Company also had state research and development tax credit carryforwards of approximately $0.2 million, which begin to expire in 2039.

Utilization of the net operating loss carryforwards and research and development tax credit carryforwards may be subject to an annual limitation under Section 382 of the Internal Revenue Code, and corresponding provisions of state law, due to ownership changes that have occurred previously or that could occur in the future. These ownership changes may limit the amount of carryforwards that can be utilized annually to offset future taxable income. In general, an ownership change, as defined by Section 382, results from transactions increasing the ownership of certain shareholders or public groups in the stock of a corporation by more than 50% over a three-year period.

The Company completed a study to assess whether an ownership change has occurred under Section 382, and determined that all net operating loss carryforwards and credits generated before September 12, 2024 are limited. As a result, the carryforwards before the ownership change date of September 12, 2024 are not available for utilization and have been written off. The carryforwards as of December 31, 2024 were generated after the ownership change on September 12, 2024. If the Company experiences a change of control, as defined by Section 382, subsequent to December 31, 2024, utilization of the net operating loss carryforwards or research and development tax credit carryforwards would be subject to an annual limitation under Section 382.

The Company files tax returns as prescribed by the tax laws of the jurisdictions in which it operates. In the normal course of business, the Company is subject to examination by federal and state jurisdictions, where applicable. There are currently no pending tax examinations. As of December 31, 2024, the Company's tax years are still open under statute from 2016 to the present.

It is the Company's policy to include penalties and interest expense related to income taxes as a component of the provision for income taxes. As of December 31, 2024 and 2023, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in the Company's statements of operations. For the year ended December 31, 2024, the Company generated research and development tax credits but has not conducted a study to document the qualified activities. This study may result in an adjustment to the Company's research and development tax credit carryforwards; however, until a study is completed and any adjustment is known, no amounts are being presented as an uncertain tax position. A full valuation allowance has been provided against the Company's research and development tax credit carryforwards and, if an adjustment is required, this adjustment would result in an adjustment to the deferred tax asset established for the research and development tax credit carryforwards and the valuation allowance.

14. Defined Contribution Plan

The Company has a defined contribution savings plan under Section 401(k) of the Internal Revenue Code (the "401(k) Plan"). The 401(k) Plan covers all employees who meet defined minimum age and service requirements, and allows participants the option to elect to defer a portion of their annual compensation on a pretax basis. As currently established, the Company is not required to make contributions to the 401(k) Plan. The Company made $0.6 million and $0.7 million in contributions to the 401(k) Plan for the years ended December 31, 2024 and 2023, respectively.

15. Net Loss per Share

The following common stock equivalents were excluded from the calculation of diluted net loss per share for the periods indicated because including them would have had an anti-dilutive effect:

	Year Ended December 31,	
	2024	2023
Stock options	9,354,699	9,972,217
Restricted stock units	43,072	75,017
Total	9,397,771	10,047,234

16. Restructuring Activities

In September 2024, the Company announced a plan to reprioritize research and development activities to focus on advancing pociredir for the treatment of sickle cell disease, novel therapeutic agents for the treatment of DBA, and the Company's early discovery programs. The plan reduced the Company's workforce from 80 to 51 full-time employees, including a reduction of positions across both research and development and general and administrative functions. During the year ended December 31, 2024, the Company recorded aggregate restructuring charges of $2.1 million related to severance and other employee-related costs, all of which were paid during the year ended December 31, 2024.

Accrued restructuring charges as of December 31, 2023	$	—
Restructuring charges incurred during the period		2,063
Amounts paid during the period		(1,686)
Accrued restructuring charges as of December 31, 2024	$	377

17. Related-Party Transactions

In August 2024, the Company entered into an exchange agreement with RA Capital, one of the Company's principal stockholders and a related party in accordance with ASC 850, *Related Party Disclosures,* pursuant to which RA Capital exchanged 8,500,000 shares of the Company's common stock, par value $0.001 per share, or common stock, for a pre-funded warrant to acquire 8,500,000 shares of the Company's common stock. No cash was exchanged related to the transaction. See Note 8, "Common Stock", for additional details of the transaction.

18. Segment Information

Segment reporting is prepared on the same basis that the Company's chief executive officer, who is the Company's chief operating decision maker (the "CODM"), utilizes to manage the business and makes decisions on how to allocate resources and assess performance of the business. The Company and the CODM view the Company's operations as a single operating segment. The Company's singular focus is on developing small molecules to improve the lives of patients with genetically defined rare diseases in areas of high unmet medical need.

The Company and the CODM primarily utilize the segment's consolidated net income (loss), disaggregated between (a) research and development and (b) general and administrative, as the key indicator to assess the segment's performance and for allocating resources.

The Company's reportable segment revenue, operating expenses, and net loss for the years ended December 31, 2024 and December 31, 2023 are as follows:

	Year Ended December 31,	
	2024	2023
Collaboration revenue	$ 80,000	$ 2,805
Operating expenses:		
Research and development		
Losmapimod external expenses	20,801	29,069
Pociredir external expenses	8,577	7,442
Employee compensation expenses (excluding stock-based compensation expenses)	15,347	16,978
Stock-based compensation expenses	4,653	3,776
Pre-development candidate expenses and unallocated expenses	14,008	14,536
General and administrative	36,448	41,668
Restructuring expenses	2,063	—
Total operating expenses	101,897	113,469
Loss from operations	(21,897)	(110,664)
Other income, net	12,172	13,329
Net loss	$ (9,725)	$ (97,335)

EXHIBIT INDEX

Exhibit Number	Description
3.1	Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K filed with the Securities and Exchange Commission on July 22, 2019).
3.2	Certificate of Amendment of the Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 to the Current Report on Form 8-K filed with the Securities and Exchange Commission on June 9, 2023).
3.3	Amended and Restated Bylaws of the Registrant (incorporated by reference to Exhibit 3.2 to the Registrant's Current Report on Form 8-K filed with the Securities and Exchange Commission on July 22, 2019).
4.1	Specimen Stock Certificate evidencing shares of common stock (incorporated by reference to Exhibit 4.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-232260) filed with the Securities and Exchange Commission on June 21, 2019).
4.2	Description of the Registrant's Securities Registered under Section 12 of the Exchange Act (incorporated by reference to Exhibit 4.2 to the Registrant's Annual Report on Form 10-K filed with the Securities and Exchange Commission on March 5, 2020).
10.1#	2016 Stock Incentive Plan, as amended (incorporated by reference to Exhibit 10.2 to the Registrant's Registration Statement on Form S-1 (File No. 333-232260) filed with the Securities and Exchange Commission on June 21, 2019).
10.2#	Form of Incentive Stock Option Agreement under the 2016 Stock Incentive Plan (incorporated by reference to Exhibit 10.3 to the Registrant's Registration Statement on Form S-1 (File No. 333-232260) filed with the Securities and Exchange Commission on June 21, 2019).
10.3#	Form of Non-Statutory Stock Option Agreement under the 2016 Stock Incentive Plan (incorporated by reference to Exhibit 10.4 to the Registrant's Registration Statement on Form S-1 (File No. 333-232260) filed with the Securities and Exchange Commission on June 21, 2019).
10.4#	Form of Restricted Stock Agreement under the 2016 Stock Incentive Plan (incorporated by reference to Exhibit 10.5 to the Registrant's Registration Statement on Form S-1 (File No. 333-232260) filed with the Securities and Exchange Commission on June 21, 2019).
10.5#	2019 Stock Incentive Plan (incorporated by reference to Exhibit 10.6 to Amendment No. 1 to Registrant's Registration Statement on Form S-1 (File No. 333-232260) filed with the Securities and Exchange Commission on July 8, 2019).
10.6#	Form of Stock Option Agreement under the 2019 Stock Incentive Plan (incorporated by reference to Exhibit 10.7 to Amendment No. 1 to Registrant's Registration Statement on Form S-1 (File No. 333-232260) filed with the Securities and Exchange Commission on July 8, 2019).
10.7#	Form of Non-Statutory Stock Option Agreement (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on November 4, 2021).
10.8#	Form of Restricted Stock Unit Agreement under the 2019 Stock Incentive Plan (incorporated by reference to Exhibit 10.10 to the Registrant's Annual Report on Form 10-K filed with the Securities and Exchange Commission on March 3, 2022).
10.9#	2019 Employee Stock Purchase Plan (incorporated by reference to Exhibit 10.8 to Amendment No. 1 to Registrant's Registration Statement on Form S-1 (File No. 333-232260) filed with the Securities and Exchange Commission on July 8, 2019).
10.10#	2022 Inducement Stock Incentive Plan (incorporated by reference to Exhibit 10.12 to the Registrant's Annual Report on Form 10-K filed with the Securities and Exchange Commission on March 3, 2022).
10.11#	First Amendment to 2022 Inducement Stock Incentive Plan (incorporated by reference to Exhibit 10.13 to the Registrant's Annual Report on Form 10-K filed with the Securities and Exchange Commission on March 9, 2023).
10.12#	Second Amendment to 2022 Inducement Stock Incentive Plan (incorporated by reference to Exhibit 10.12 to the Registrant's Annual Report on Form 10-K filed with the Securities and Exchange Commission on February 27, 2024).
10.13#	Third Amendment to 2022 Inducement Stock Incentive Plan, effective as of June 17, 2024 (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on July 31, 2024).
10.14#	Form of Non-Statutory Stock Option Agreement under 2022 Inducement Stock Incentive Plan (incorporated by reference to Exhibit 10.13 to the Registrant's Annual Report on Form 10-K filed with the Securities and Exchange Commission on March 3, 2022).

10.15#	Form of Restricted Stock Unit Agreement under 2022 Inducement Stock Incentive Plan (incorporated by reference to Exhibit 10.14 to the Registrant's Annual Report on Form 10-K filed with the Securities and Exchange Commission on March 3, 2022).
10.16#*	Summary of Non-Employee Director Compensation Program.
10.17#	Form of Employment Agreement for Executive Officers (incorporated by reference to Exhibit 10.12 to Amendment No. 1 to Registrant's Registration Statement on Form S-1 (File No. 333-232260) filed with the Securities and Exchange Commission on July 8, 2019).
10.18#	Employment Agreement, dated May 12, 2023, by and between Registrant and Alex C. Sapir (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on August 3, 2023).
10.19#	Employment Agreement, dated August 7, 2023, by and between the Registrant and Alan A. Musso (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on November 7, 2023).
10.20#	Employment Agreement, dated October 29, 2020, by and between the Registrant and Curtis Oltmans (incorporated by reference to Exhibit 10.16 to the Registrant's Annual Report on Form 10-K filed with the Securities and Exchange Commission on March 4, 2021).
10.21#	Employment Agreement, dated March 18, 2024, by and between the Registrant and Patrick Horn (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on May 13, 2024).
10.22#	Form of Indemnification Agreement between the Registrant and each of its Executive Officers and Directors (incorporated by reference to Exhibit 10.15 to Registrant's Registration Statement on Form S-1 (File No. 333-232260) filed with the Securities and Exchange Commission on June 21, 2019).
10.23†	Collaboration and License Agreement, dated as of July 20, 2020, by and between the Registrant and MyoKardia, Inc, a wholly-owned subsidiary of Bristol-Myers Squibb Company (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-38978) filed with the Securities and Exchange Commission on November 10, 2020).
10.24†	First Amendment to Collaboration and License Agreement, effective as of April 20, 2023, by and between the Registrant and MyoKardia, Inc, a wholly-owned subsidiary of Bristol-Myers Squibb Company (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on August 3, 2023).
10.25†	Second Amendment to Collaboration and License Agreement, effective as of July 24, 2024, by and between the Registrant and MyoKardia, Inc, a wholly-owned subsidiary of Bristol Myers Squibb Company (incorporated by reference to Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on July 31, 2024).
10.26†	License Agreement, effective as of July 5, 2023, by and between the Registrant and CAMP4 Therapeutics Corporation (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on November 7, 2023).
10.27†	Collaboration and License Agreement, dated as of May 11, 2024, by and between the Registrant and Genzyme Corporation, Inc, a wholly-owned subsidiary of Sanofi (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on July 31, 2024).
10.28	Lease for 26 Landsdowne Street, dated November 22, 2017, by and between the UP 26 Landsdowne, LLC and the Registrant (incorporated by reference to Exhibit 10.11 to the Registrant's Registration Statement on Form S-1 (File No. 333-232260) filed with the Securities and Exchange Commission on June 21, 2019).
10.29	Controlled Equity Offering℠ Sales Agreement, dated February 27, 2024, by and among the Registrant, Cantor Fitzgerald & Co. and Stifel, Nicolaus & Company, Incorporated (incorporated by reference to Exhibit 1.2 to the Registrant's Registration Statement on Form S-3 filed with the Securities and Exchange Commission on February 27, 2024).
10.30	Form of Pre-Funded Warrant (incorporated by reference to Exhibit 4.1 to the Registrant's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on November 13, 2024).
19.1*	Insider Trading Policy of Registrant.
21.1	Subsidiary of the Registrant (incorporated by reference to Exhibit 21.1 to the Registrant's Annual Report on Form 10-K filed with the Securities and Exchange Commission on February 27, 2024).
23.1*	Consent of Ernst & Young LLP, independent registered public accounting firm.
31.1*	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.

31.2*	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1+	Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
32.2+	Certification of Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
97.1#	Compensation Recovery Policy of Registrant (incorporated by reference to Exhibit 97.1 to the Registrant's Annual Report on Form 10-K filed with the Securities and Exchange Commission on February 27, 2024).
101.INS	XBRL Instance Document - the instance document does not appear in the Interactive Data File as its XBRL tags are embedded within the Inline XBRL document
101.SCH	Inline XBRL Taxonomy Extension Schema With Embedded Linkbase Documents
104	Cover Page formatted as Inline XBRL and contained in Exhibit 101

# Indicates a management contract or any compensatory plan, contract or arrangement.

† Certain portions of this exhibit have been omitted because the registrant has determined that they are both not material and is the type of information that the registrant treats as private or confidential.

* Filed herewith.

+ Furnished herewith.

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**.**

Fulcrum Therapeutics, Inc.

Date: February 25, 2025

By: /s/ Alex C. Sapir
Alex C. Sapir
President and Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this report has been signed below by the following persons on behalf of the registrant in the capacities and on the dates indicated.

Name	Title	Date
/s/ Alex C. Sapir Alex C. Sapir	President and Chief Executive Officer (Principal Executive Officer)	February 25, 2025
/s/ Alan Musso Alan Musso	Chief Financial Officer (Principal Financial Officer)	February 25, 2025
/s/ Greg Tourangeau Greg Tourangeau	Vice President, Finance (Principal Accounting Officer)	February 25, 2025
/s/ Kate Haviland Kate Haviland	Chairman of the Board	February 25, 2025
/s/ Sonja Banks Sonja Banks	Director	February 25, 2025
/s/ Katina Dorton Katina Dorton	Director	February 25, 2025
/s/ Alan Ezekowitz Alan Ezekowitz, MBChB, D. Phil	Director	February 25, 2025
/s/ James Geraghty James Geraghty	Director	February 25, 2025
/s/ Robert J. Gould Robert J. Gould, Ph.D.	Director	February 25, 2025
/s/ Colin Hill Colin Hill	Director	February 25, 2025
/s/ Rachel K. King Rachel K. King	Director	February 25, 2025