UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

FORM 10-K

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

For the fiscal year ended December 31, 2023

☐ **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 001-37722

SPYRE THERAPEUTICS, INC.

(Exact name of Registrant as specified in its charter)

Delaware	**46-4312787**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**
221 Crescent Street Building 23, Suite 105 Waltham, MA	**02453**
(Address of Principal Executive Offices)	**(Zip Code)**

Registrant's Telephone Number, including area code: (617) 651-5940
Securities registered pursuant to Section 12(b) of the Exchange Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 Par Value Per Share	SYRE	The Nasdaq Stock Market LLC (Nasdaq Global Select Market)

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

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

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

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

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

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

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

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

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

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

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

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

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the Registrant on June 30, 2023 (the last business day of the Registrant's second fiscal quarter), based upon the closing price of $11.2625 of the Registrant's common stock as reported on The Nasdaq Global Market, was approximately $26.2 million.

Indicate the number of shares outstanding of each of the Registrant's classes of common stock, as of the latest practicable date.

Class	Outstanding at February 21, 2024
Common stock, $0.0001 par value per share	36,150,941 shares

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's Definitive Proxy Statement ("Proxy Statement") relating to the 2024 Annual Meeting of Stockholders will be filed with the Commission within 120 days after the end of the Registrant's 2023 fiscal year and is incorporated by reference into Part III of this Report.

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NOTE ABOUT FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, or Annual Report, contains forward-looking statements within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, and Section 27A of the Securities Act of 1933, as amended, or the Securities Act. All statements contained in this Annual Report other than statements of historical fact, including statements regarding stockholder approval of the conversion rights of our Series B preferred stock, par value $0.0001 (the "Series B Preferred Stock"); any future payouts under our contingent value rights ("CVRs") issued in connection with the Asset Acquisition (as defined herein); our ability to achieve the expected benefits or opportunities and related timing with respect to our acquisition of Spyre Therapeutics, Inc. (“Pre-Merger Spyre”) or to monetize our legacy assets, our future results of operations and financial position, business strategy, the length of time that we believe our existing cash resources will fund operations, market size, potential growth opportunities, preclinical and future clinical development activities, efficacy and safety profile of our product candidates, potential therapeutic benefits and economic value of our product candidates, use of net proceeds from our public offerings, the timing and results of preclinical studies and clinical trials, the expected impact of macroeconomic conditions, including inflation, increasing interest rates and volatile market conditions, current or potential bank failures, as well as global events, including the ongoing military conflict in Ukraine, conflict in Israel and surrounding areas, and geopolitical tensions in China on our operations, and the receipt and timing of potential regulatory designations, approvals and commercialization of product candidates, are forward-looking statements. The words “believe,” “may,” “will,” “potentially,” “estimate,” “continue,” “anticipate,” “predict,” “target,” “intend,” “could,” “would,” “should,” “project,” “plan,” “expect,” and similar expressions that convey uncertainty of future events or outcomes are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including those described in Item 1A, “Risk Factors” and elsewhere in this Annual Report. Moreover, we operate in a very competitive and rapidly changing environment, and new risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. In light of these risks, uncertainties, and assumptions, the forward-looking events and circumstances discussed in this Annual Report may not occur and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements.

You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee that the future results, levels of activity, performance or events and circumstances reflected in the forward-looking statements will be achieved or occur. We undertake no obligation to update publicly any forward-looking statements for any reason after the date of this report to conform these statements to actual results or to changes in our expectations, except as required by law. You should read this Annual Report with the understanding that our actual future results, levels of activity, performance and events and circumstances may be materially different from what we expect.

Unless the context indicates otherwise, as used in this Annual Report, the terms “Spyre,” "Aeglea BioTherapeutics, Inc.," “the Company,” “we,” “us,” and “our” refer to Spyre Therapeutics, Inc., a Delaware corporation, and its consolidated subsidiaries taken as a whole. “Spyre” and all product candidate names are our common law trademarks. This Annual Report contains additional trade names, trademarks and service marks of other companies, which are the property of their respective owners. We do not intend our use or display of other companies’ trade names, trademarks or service marks to imply a relationship with, or endorsement or sponsorship of us by, these other companies.

All references to “our product candidates,” “our programs” and “our pipeline” in this Annual Report refer to the research programs with respect to which we have exercised the option to acquire intellectual property license rights to or have the option to acquire intellectual property license rights to pursuant to that certain antibody discovery and option agreement, dated May 25, 2023 and subsequently amended and restated on September 29, 2023, by and among Spyre Therapeutics, LLC, Paragon Therapeutics, Inc. (“Paragon”) and Parapyre Holding LLC (“Parapyre”) (the “Paragon Agreement”).

Please be advised that on September 8, 2023, we effected a reverse stock split of our common stock at a ratio of 1-for-25 (the “Reverse Split”). Except as indicated otherwise, all share numbers related to our common stock disclosed in this Annual Report have been adjusted on a post-Reverse Split basis. In addition, on November 28, 2023, we changed our name from “Aeglea BioTherapeutics, Inc.” to “Spyre Therapeutics, Inc.”

PART I

ITEM 1. BUSINESS

Company Overview

On June 22, 2023, we acquired Pre-Merger Spyre (the "Asset Acquisition") pursuant to the Agreement and Plan of Merger (the "Acquisition Agreement"), by and among us, Aspen Merger Sub I, Inc., a Delaware corporation and a wholly owned subsidiary of the Company (“First Merger Sub”), Sequoia Merger Sub II, LLC, a Delaware limited liability company and one of our wholly owned subsidiaries (“Second Merger Sub”), and Pre-Merger Spyre. Pre-Merger Spyre was a pre-clinical stage biotechnology company that was incorporated on April 28, 2023 under the direction of Peter Harwin, a Managing Member of Fairmount Funds Management LLC ("Fairmount"), for the purpose of holding rights to certain intellectual property being developed by Paragon. Fairmount is a founder of Paragon.

Through the Asset Acquisition, we received the option to license the intellectual property rights related to four research programs (collectively, the "Option") pursuant to the Paragon Agreement. On July 12, 2023 we exercised the Option with respect to one of these research programs to exclusively license intellectual property rights related to such research program directed to antibodies that selectively bind to α4β7 integrin and methods of using these antibodies, including methods of treating inflammatory bowel disease ("IBD") using the SPY001 program. If this research program is pursued non-provisionally and matures into issued patents, we would expect those patents to expire no earlier than 2044, subject to any disclaimers or extensions. On December 14, 2023, we exercised the Option under the Paragon Agreement to be granted an exclusive license to all of Paragon’s rights, title and interest in and to intellectual property rights, including inventions, patents, sequence information and results, under SPY002, Spyre's TL1A program, to develop and commercialize antibodies and products worldwide in all therapeutics disorders. The license agreements pertaining to such research programs are currently being finalized. Furthermore, as of the date of this Annual Report, the Option remains unexercised with respect to the intellectual property rights related to the two remaining research programs under the Paragon Agreement. For more information on the Paragon Agreement, see discussion under the heading “Paragon Agreement” below.

On July 27, 2023, we announced that we entered into an agreement to sell the global rights to pegzilarginase, an investigational treatment for the rare metabolic disease Arginase 1 Deficiency, to Immedica for $15.0 million in upfront cash proceeds and up to $100.0 million in contingent milestone payments (the "Immedica APA"). The sale of pegzilarginase to Immedica supersedes and terminates the license agreement between us and Immedica dated March 2021. See the section titled “Recent Developments” below for more information regarding the Immedica APA.

Following the Asset Acquisition and the entry into the Immedica APA, we have significantly reshaped the business into a preclinical stage biotechnology company focused on developing next generation therapeutics for patients living with IBD, including ulcerative colitis (“UC”) and Crohn’s disease (“CD”). Through the Paragon Agreement, our portfolio of novel and proprietary monoclonal antibody product candidates has the potential to address unmet needs in IBD care by improving efficacy, safety, and/or dosing convenience relative to products currently available or product candidates in development. We have engineered our product candidates with the aim to bind potently and selectively to their target epitopes and to exhibit extended pharmacokinetic half-lives through modifications in the Fc domain that increase affinity to human FcRn and increase antibody recycling. We anticipate that half-life extension will enable less frequent administration compared to marketed or development-stage mAbs that do not incorporate half-life extension modifications. Nonetheless, the drug and/or device development process is inherently uncertain, our development approach is unproven, the preclinical evidence that supports our proposed development program is preliminary and limited, and we have not yet tested any product candidate in humans. In addition to development of our product candidates as potential monotherapies, we plan to investigate combinations of our proprietary antibodies in preclinical and clinical studies to evaluate whether combination therapy (co-administration or co-formulation of multiple monoclonal antibodies) can lead to greater efficacy compared to monotherapies in IBD. We also intend to examine patient selection strategies via complementary diagnostics utilized in our clinical studies to evaluate whether patients can be matched to the optimal therapy based on genetic background and/or other biomarker signatures. We intend to deliver our product candidates through convenient, infrequently dosed, self-administered, subcutaneous injection, although the specific delivery mechanism or technology has not been selected given our early stage. Notwithstanding our efforts to develop safe and effective monotherapies and

combination therapies, there can be no guarantee that we will be able to develop product candidates that will be found to be safe and effective so as to obtain the necessary regulatory approvals to market our product candidates.

Our Strategy

Our goal is to develop next-generation therapeutics for the treatment of IBD, relying on three strategic pillars:

- Advancing novel, long-acting antibodies against validated IBD targets,
- Evaluating rational therapeutic combinations of our long-acting antibodies, and
- Developing genetic- or biomarker-based complementary diagnostics (e.g., a medical device that provides valuable information about whether a treatment might be beneficial, but is not required for the administration of the drug) to match treatment targets to IBD sub-populations. See the heading “Our Precision Immunology Approach” below for additional information.

Our Half-Life Extension Approach

A drug’s half-life is an indicator of how long the therapy remains in the body and is a measure of the period of time it takes for the concentration of a drug in the blood to be reduced by half. The half-life determines how frequently a drug needs to be administered to maintain its therapeutic effect. Technologies that extend half-life for injectable products reduce the frequency of injections, or number of injections per applicable time period, needed to provide a therapeutic benefit.

All of our antibody programs are engineered to increase FcRn binding in order to prolong the half-life via increased FcRn-mediated endosomal recycling (rather than catabolism) efficiency. Mutagenesis of the antibody Fc domain, such as the YTE and LS mutations, has been shown to increase binding affinity to human FcRn by more than ten-fold and result in >two-fold the half-life in cynomolgus monkeys (Haraya and Tachibana 2022). Additionally, several antibodies incorporating YTE or LS mutations have been tested in humans and exhibit prolonged half-lives, including at least two FDA-approved products (Beyfortus ®, Evushield ®).

Engineered mAbs with increased half-life have the potential to confer more favorable dosing profiles, including lower dosing frequencies and/or lower required doses administered. In our head-to-head NHP studies, SPY001 and SPY002 exhibited a greater than three-fold and two to three-fold increase in half-life, respectively, relative to comparator antibodies that lack half-life extension modifications. Allometric scaling of the NHP pharmacokinetics to humans support the potential for every other month or quarterly SC dosing for these antibodies, which we believe is a significant improvement over every two week or monthly SC dosing of competitor programs.

Our Combination Therapy Approach

In addition to the development of our product candidates as potential monotherapies, we also plan to investigate combinations of our proprietary antibodies in preclinical studies in 2024 and in a clinical study that will include combinations in 2025, subject to approval of an IND or equivalent foreign regulatory submission, to evaluate whether combination therapy (co-administration or co-formulation of multiple monoclonal antibodies) can lead to greater efficacy compared to monotherapies in IBD. This is expected to include SPY120, which combines SPY001 (α4ß7) and SPY002 (TL1A), following approval of an IND or equivalent foreign regulatory submission anticipated in 2025. This is anticipated to be followed by combinations that include SPY003 (IL-23), SPY130 (a combination of SPY001 and SPY003) and SPY230 (a combination of SPY002 and SPY003). We believe that combinations targeting distinct pathways could lead to greater efficacy in IBD. To support our plans, this year we intend to evaluate our combination regimens in preclinical in vitro and in vivo pharmacology models and to conduct combination toxicology studies.

Our Precision Immunology Approach

We aim to develop genetic- or biomarker-based patient selection approaches such as complementary diagnostics that utilize a genomic or proteomic signature across our portfolio of therapeutics to aid patients and

physicians in selecting the optimal treatment regimen. We are in discussions with potential partners to develop patient selection strategies for each of our targets, and if successful, we would intend to evaluate such approaches in Phase 2 studies in IBD patients. Depending on their performance, one or more of such approaches could be utilized in Phase 3 studies and potentially commercially as complementary diagnostics.

A complementary diagnostic is a medical device, often an in vitro device, which provides information that is valuable for the safe and effective use of a corresponding therapeutic drug or biologic product. In contrast, a companion diagnostic is considered *essential* for the safe and effective use of a corresponding drug or biological product. A complementary diagnostic can be used to identify patients or subsets of patients who are most likely to benefit from the therapeutic product, but unlike a companion diagnostic, is not required prior to administration or prescription of a drug. A complementary diagnostic is generally developed in conjunction with the clinical program for an associated therapeutic product and would require additional subgroup analysis as a secondary or exploratory endpoint from patient samples (e.g., blood, saliva) provided in the trial. The development path of a complementary diagnostic may include additional meetings with regulatory authorities, such as a pre-submission meeting and the requirement to submit an investigational device exemption application. As a result, the overall timing and cost of our clinical development program, and ultimately our commercial strategy, may be impacted by our pursuit of complementary diagnostics.

Commercial use of a complementary diagnostic may require additional regulatory approvals, but we do not expect the approval and commercialization of any of our therapeutic product candidates to be dependent on regulatory approval or the commercialization of a diagnostic. A complementary diagnostic could be useful in a commercial setting to facilitate first line use of a therapeutic for patients who are diagnostic-positive and are deemed more likely to respond, as long as diagnostic-negative patients (e.g., false-negatives) are not unduly burdened with access restrictions.

Inflammatory Bowel Disease

IBD is a chronic condition characterized by inflammation within the gastrointestinal tract. It encompasses two main disorders: UC and CD. UC primarily affects the colon and the rectum. Inflammation occurs in the innermost lining of the colon. Symptoms include bloody diarrhea, abdominal pain, bowel urgency, and frequent bowel movements. CD can affect any part of the gastrointestinal tract, from the mouth to the anus. It is characterized by inflammation that extends through multiple layers of the bowel wall. Symptoms include abdominal pain, diarrhea, weight loss, fatigue, and complications such as strictures or fistulas. Both conditions can significantly impact patients' quality of life in terms of physical health, emotional well-being, and the unpredictability of symptom onset.

IBD affects millions of individuals worldwide, with increasing prevalence and incidence in both developed and developing countries. In the United States, it is estimated that approximately 2.4 million individuals currently have IBD, with approximately 70,000 patients newly diagnosed every year. Based on research from the Crohn's and Colitis Foundation of America, the market for IBD therapeutics is expected to experience steady growth, driven by rising disease prevalence, increasing diagnosis rates, and evolving treatment paradigms.

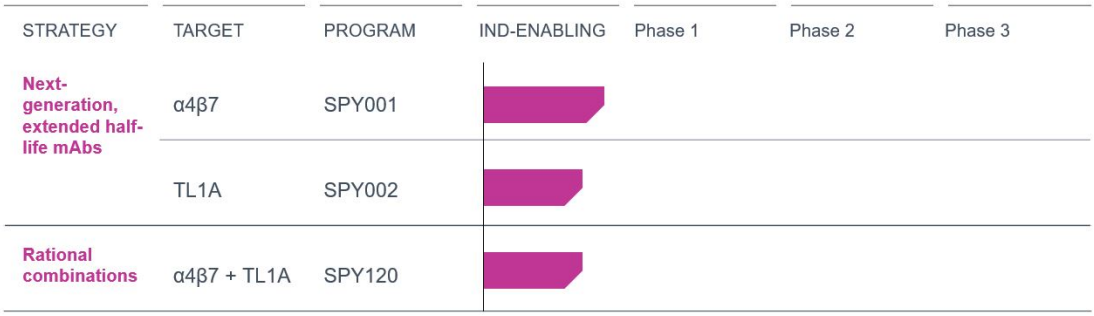
A range of pharmaceutical options exists, including anti-inflammatory drugs, immunosuppressants, and biologics. Treatment plans are often tailored to the individual patient's disease severity, location, and response to therapy. In some cases, surgical interventions such as bowel resection or ostomy formation may be necessary to manage complications or improve quality of life.

Despite available treatments, there remain substantial unmet needs in IBD management, including:

- Inadequate response or loss of response to existing therapies,
- Side effects and safety concerns associated with long-term medication use,
- Limited options for patients with refractory or severe disease, and
- Adherence to frequent and/or inconvenient dosing regimens.

Our Portfolio

We are advancing a pipeline of monoclonal antibodies ("mAbs") for the treatment of IBD (UC and CD) in connection with the research programs with respect to which we have exercised the Option to exclusively license all of Paragon's right, title, and interest in, including all intellectual property license rights to, or have the Option to acquire such intellectual property and other rights to pursuant to the Paragon Agreement and plan to develop patient selection approaches for each program. The following table summarizes the programs that have been exercised to date pursuant to the Paragon Agreement:



Other early-stage programs:

- SPY003 – anti-IL-23 mAb
- SPY004 – novel MOA mAb
- SPY130 – combination anti-α4ß7 and anti-IL-23 mAbs
- SPY230 – combination anti-TL1A and anti-IL-23 mAbs

We have nominated development candidates for SPY001 and SPY002. We have exercised our Option to license worldwide rights from Paragon for the SPY001 and SPY002 programs and the SPY001 License Agreement and SPY002 License Agreement are currently being finalized with execution expected to occur in the first half of 2024. We continue to hold the Option to license similar rights from Paragon for certain other programs. We expect the SPY003 license to be restricted to IBD, and we expect other potential program licenses related to the Option to be indication agnostic. We additionally have an exclusive option under the agreement for a discovery stage program targeting a novel MOA that also incorporates half-life extension (SPY004). See the section titled "Paragon Agreement" for more information on the Paragon Agreement, including the Option.

Although we hold the Option to acquire intellectual property license rights related to the SPY003 and SPY004 programs, such Option remains unexercised.

The drug and/or device development process is inherently uncertain, our development approach is unproven, the preclinical evidence that supports our proposed development program is preliminary and limited, and we have not yet tested any product candidate in humans. Notwithstanding our efforts to develop safe and effective monotherapies and combination therapies, there can be no guarantee that we will be able to develop product candidates that will be found to be safe and effective so as to obtain the necessary regulatory approvals to market our product candidates.

For a discussion of the risks associated with our portfolio, see the section of this report entitled "Risk Factors."

SPY001 – anti-α4β7 mAb

Our most advanced product candidate, SPY001, is a highly potent, highly selective, and fully human monoclonal immunoglobulin G1 antibody designed to bind selectively to the α4β7 integrin being developed for the treatment of IBD (UC and CD). The α4β7 integrin is a protein found on the surface of immune cells known as lymphocytes. This integrin regulates the migration of lymphocytes to the gut where they contribute to the inflammatory process in IBD. By selectively binding to the α4β7 integrin, SPY001 is designed to prevent the

interaction of these lymphocytes with MAdCAM-1, a molecule expressed on endothelial cells lining the blood vessels in the gut. This interaction is responsible for guiding lymphocytes from the bloodstream into the gut tissue, where they cause inflammation. By blocking the interaction between α4β7 integrin and MAdCAM-1, SPY001 aims to reduce the recruitment of lymphocytes to the gut, leading to a decrease in inflammation. Since it specifically targets the gut immune system, SPY001 is designed to minimize systemic immunosuppressive effects unrelated to IBD pathology.

SPY001 is being developed by us and our research partners at Paragon. Prior to the closing of the Asset Acquisition, Paragon had sole leadership in conducting *in vitro* and *in vivo* studies for SPY001 clones, including the potency, selectivity, and NHP PK data supporting development candidate nomination for the SPY001 program. Following the closing of the Asset Acquisition and the exercise of the Option with respect to the SPY001 program, Spyre and Paragon established a Joint Development Committee (“JDC”) comprised of two employees from Spyre and two employees from Paragon and jointly directed research and development work, with Spyre having final decision rights on the budget for any research program. The JDC is the decision-making body for SPY001 and our other pipeline programs prior to the execution of the SPY-001 License Agreement and, in addition to SPY001, we will also control and lead the development process for each of SPY002, non-optioned programs SPY003 and SPY004, and each of the combination programs once the respective license agreements are executed.

SPY001 preclinical characterization studies were conducted in-house with support from third party vendors. SPY001 demonstrates similar potency and selectivity as vedolizumab in preclinical *in vitro* models including surface plasmon residence (n=5 concentrations, study completed September 2023) and cellular adhesion assays (see Figure 1, n=6 replicates per group, study completed in August 2023). It also incorporates a half-life extending modification resulting in an increase in half-life of >three-fold in Tg276 transgenic mice that express human FcRn (n=5 per group, studies completed in August 2023) and an increase in half-life of >three-fold in NHPs (n=6 per group, studies completed in December 2023), compared to vedolizumab (see Figure 2).

SPY001 is currently progressing through IND-enabling studies (chemistry, manufacturing, and controls ("CMC") scale-up complete, IND-enabling toxicology studies initiating), and we expect to submit an IND or equivalent foreign regulatory submission and enter a Phase 1 first-in-human ("FIH") study in healthy volunteers in the first half of 2024, pending health agency approval. Interim data from the Phase 1 healthy volunteer study are expected by the end of 2024. If successful, SPY001 would then advance to Phase 2 clinical studies and, pending further success, Phase 3 clinical studies to support global regulatory submissions and commercial approval.

Figure 1. Potency and selectivity of SPY001 relative to vedolizumab in cellular assays.

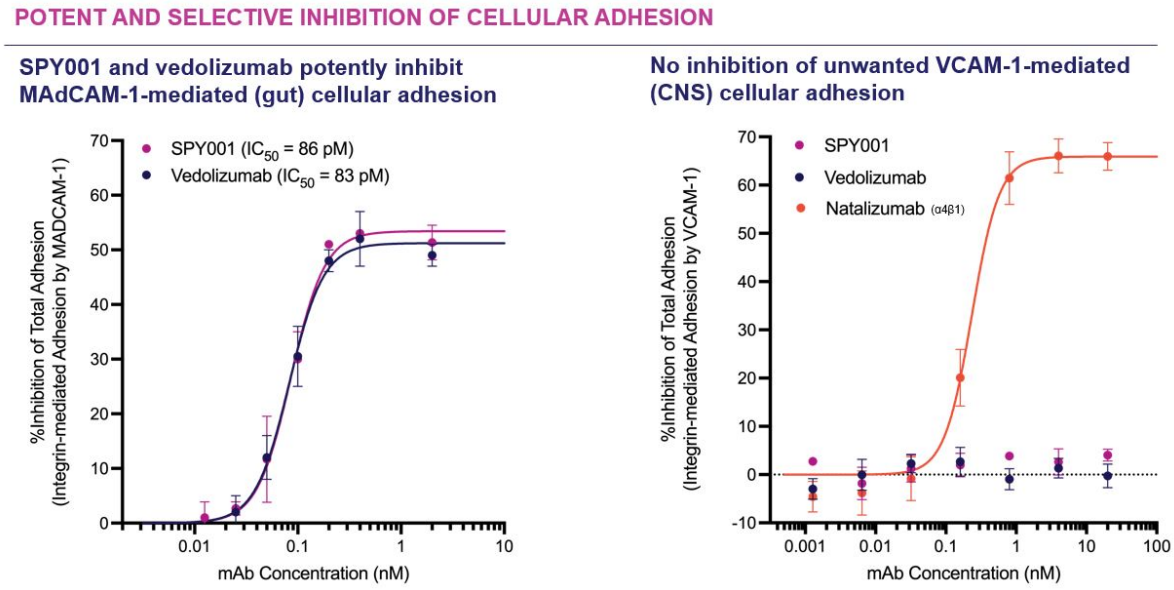
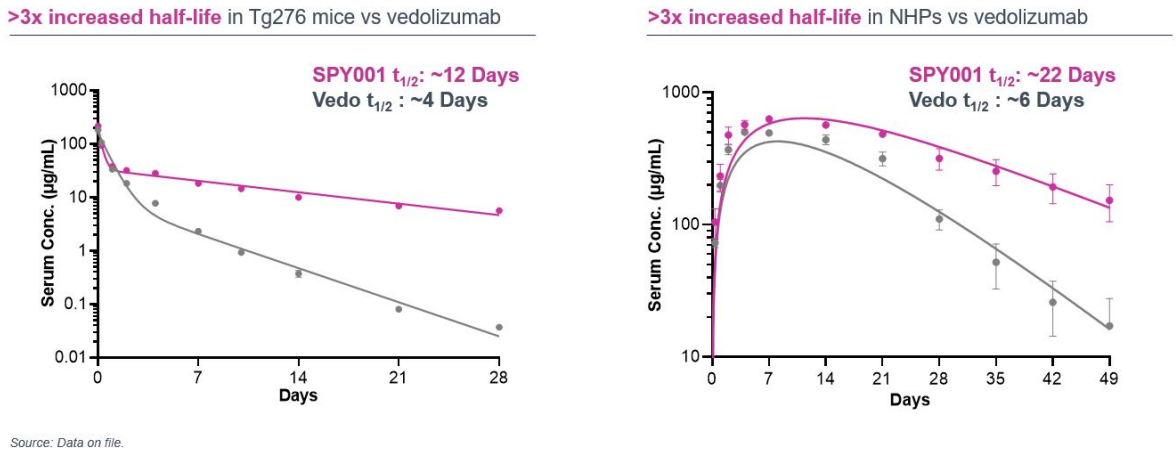


Figure 2. Pharmacokinetic concentration-time curves of SPY001 compared to vedolizumab in Tg276 transgenic mice and non-human primates (n=3-5 per group shown, removing primates that developed anti-drug antibodies).



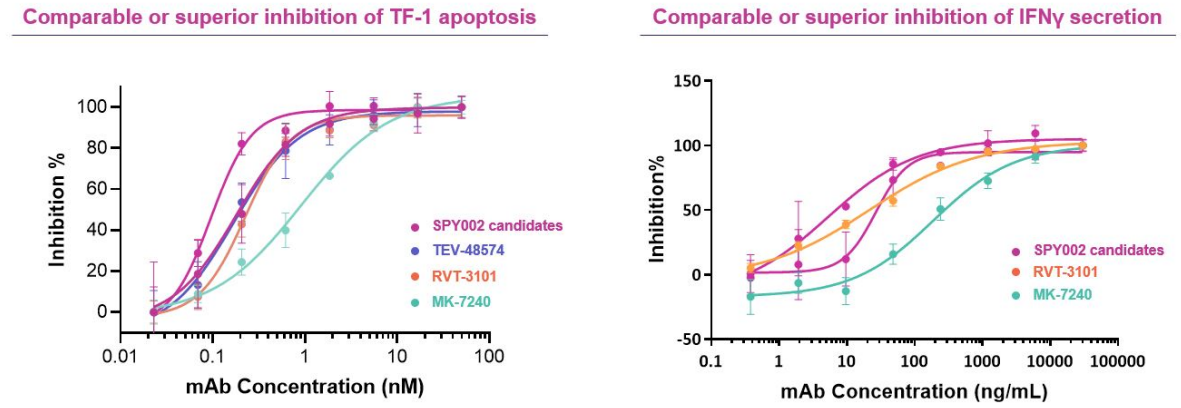
Source: Data on file.

SPY002 – anti-TL1A mAb

For our co-lead program, SPY002, we have nominated two highly potent, highly selective, and fully human mAb candidates designed to bind to tumor necrosis factor-like ligand 1A (“TL1A”), both of which are in preclinical development for the treatment of IBD (UC and CD). TL1A is a protein that plays a role in regulating the immune system and is elevated in the gut tissue of individuals with IBD. TL1A interacts with its receptor, death receptor 3 (“DR3”), which is expressed in various immune cells, including T cells. This interaction triggers signaling pathways that contribute to inflammation and immune system activation, leading to IBD symptomology. The SPY002 candidates have been designed to block the interaction between TL1A and DR3, and thereby inhibit the downstream signaling events and dampen the inflammatory response. By neutralizing TL1A, we believe SPY002 candidates have the potential to modulate the immune response in IBD patients, potentially reducing disease activity and promoting mucosal healing.

SPY002 preclinical characterization studies were conducted in-house with support from third party vendors. Our extensive discovery campaign has identified two lead candidates which bind TL1A monomers and trimers and have subnanomolar potency in cellular assays (see Figure 3, n=4 replicates per group per study, studies completed in Q42023 and Q12024). The candidates also exhibited extended pharmacokinetic half-lives of greater than two to three-fold relative to competitive molecules in clinical development that do not incorporate half-life extending modifications, based on head-to-head preclinical studies in NHPs (see Figure 4, n=5 per group, studies completed in Q42023 and Q12024). SPY002 candidates are currently progressing through IND-enabling studies (CMC scale-up ongoing) and we expect to submit an IND or equivalent foreign regulatory submission and enter a Phase 1 FIH study in healthy volunteers in the second half of 2024, with one or both of our SPY002 candidates pending additional preclinical data and pending health agency approval. Interim data from the Phase 1 healthy volunteer study are expected in the first half of 2025. If successful, one SPY002 candidate would then advance to Phase 2 clinical studies and, pending further success, Phase 3 clinical studies to support global regulatory submissions and commercial approval.

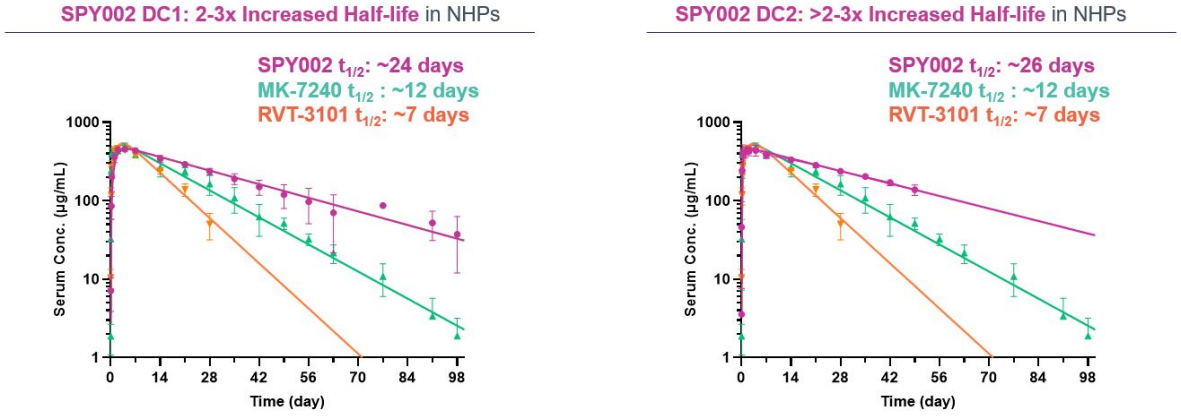
Figure 3. Inhibition of TL1-A induced TF-1 cell apoptosis (left) and IFNγ secretion in primary human whole blood 1 donor of 4 donors profiled (right).



Note: Inhibition of TL1A-induced TF-1 cell apoptosis (left) and IFNg secretion in primary human whole blood 1 donor of 4 donor profiled (right).

Source: Data on file

Figure 4. Pharmacokinetic concentration-time curves of SPY002 candidates compared to competing anti-TL1A molecules in non-human primates.



Source: Data on file.

SPY003 – anti-IL-23 mAb

SPY003 is a discovery-stage program focused on designing antibodies to bind to Interleukin 23 (“IL-23”) and incorporates half-life extending modifications. IL-23 is a cytokine that is produced by immune cells and is involved in immune response regulation. IL-23 promotes the survival, expansion, and activity of Th17 cells. Th17 cells produce inflammatory cytokines, such as IL-17, which contribute to the inflammation seen in IBD. IL-23 also helps in the recruitment and activation of other immune cells, such as neutrophils, which further contribute to tissue damage in the gut. To date, we have identified several promising clones that meet our target product profile, and we are in the process of narrowing down the potential clones to select a development candidate based on pharmacokinetic performance and CMC developability. We are continuing our preclinical development efforts with the SPY003 program and expect to nominate a development candidate in mid-2024 and move into IND-enabling studies in the second half of 2024. Upon development candidate nomination, we intend to exercise our Option to acquire intellectual property rights for the SPY003 program pursuant to the Paragon Agreement.

SPY004 – novel MOA mAb

SPY004 is an undisclosed novel mechanism of action ("MOA") and incorporates half-life extension modifications. Upon development candidate nomination, we intend to exercise our Option to acquire intellectual property rights for the SPY004 program pursuant to the Paragon Agreement.

SPY120 - combination, anti-α4β7 and anti-TL1A mAbs

SPY120 combines SPY001 (anti-α4β7) and SPY002 (anti-TL1A) antibodies, pairing two mechanisms studied in third-party clinical trials targeting non-overlapping sites of action. We are currently evaluating SPY120 in preclinical studies, and plan to initiate combination toxicology studies in 2024. We expect to initiate clinical studies for SPY120 in 2025, pending approval of an IND or equivalent foreign regulatory submission anticipated in 2025.

SPY130 - combination anti-α4β7 and anti-IL-23 mAbs

SPY130 combines SPY001 (anti-α4ß7) and SPY003 (anti-IL-23) antibodies, pairing two commercially validated mechanisms targeting non-overlapping sites of action. We are currently evaluating SPY130 in preclinical studies and plan to initiate combination toxicology studies in 2025.

SPY230 – combination anti-TL1A and anti-IL-23 mAbs

SPY230 combines SPY002 (anti-TL1A) and SPY003 (anti-IL-23) antibodies, pairing two complementary mechanisms of action with potential to address overlapping and non-overlapping triggers of inflammation. We are currently evaluating SPY230 in preclinical studies and plan to initiate combination toxicology studies in 2025.

Employees and Human Capital Resources

As of December 31, 2023, we had 30 employees, all of whom were employed full time. We also engage temporary employees and consultants to augment our existing workforce. None of our employees are represented by a labor union or covered under a collective bargaining agreement. We consider our relationship with our employees to be good.

We recognize that attracting, motivating, and retaining talent at all levels is vital to continuing our success. We invest in our employees through high-quality benefits, professional development opportunities, and various health and wellness initiatives and offer competitive compensation packages (base salary and incentive plans), ensuring fairness in internal compensation practices. The principal purposes of our incentive plans (bonus and equity) are to align with the long-term interests of our stakeholders and stockholders.

Commercial

Should any of our product candidates be approved for commercialization, we intend to develop a plan to commercialize them in the United States and other key markets, through internal infrastructure and/or external partnerships in a manner that will enable us to realize the full commercial value of our product candidates. Given our stage of development, we have not yet established a commercial organization or distribution capabilities.

Manufacturing

We do not currently own or operate facilities for product manufacturing, testing, storage, and distribution. We are currently in the process of novating certain agreements with third parties for the performance of future clinical manufacturing and development activities from Paragon to us. The initial forms of these agreements are generally non-specific master services agreements that allow an entity to begin the process of future manufacturing or development services, respectively. As clinical development activities are commenced by us, the agreements will be revised to provide for the specific deliverables and associated costs that are needed under our development plan.

Pursuant to a Novation Agreement dated September 19, 2023 (the “Novation Agreement”), by and between us, Paragon and WuXi Biologics (Hong Kong) Limited (“WuXi Biologics”), we novated (i) a Biologics Master Services Agreement (the “WuXi Biologics MSA”) and (ii) a Cell Line License Agreement (the “Cell Line License Agreement”).

In light of the recently introduced BIOSECURE Act, which would prohibit federal agencies from entering into procurement contracts with an entity that uses biotechnology equipment or services from a biotechnology company of concern, we have taken several measures to strengthen our supply chain in the event that WuXi Biologics or one of our other manufacturers is impacted. We intend to establish domestic inventory of key materials and are accelerating our clinical resupply campaigns to ensure we have a sufficient stockpile of drug substance in the United States. We will also continue to closely monitor geopolitical risk and implement additional mitigations and supply chain redundancies, as needed. See the risk factor entitled “*We currently rely, and plan to rely in the future, on third parties to conduct and support our preclinical studies and clinical trials. If these third parties do not properly and successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval of or commercialize our product candidates.*”

Biologics Master Services Agreement

In April 2023, Paragon and WuXi Biologics entered into the WuXi Biologics MSA, which was subsequently novated to us by Paragon on September 19, 2023 pursuant to the Novation Agreement. The WuXi Biologics MSA governs certain development activities and Good Manufacturing Practice ("GMP") manufacturing and testing for the SPY001 program, as well as potential future programs, on a work order basis. Under the

WuXi Biologics MSA, we are obligated to pay WuXi Biologics a service fee and all non-cancellable obligations in the amount specified in each work order associated with the agreement for the provision of services.

The WuXi Biologics MSA terminates on the later of (i) June 20, 2027 or (ii) the completion of services under all work orders executed by the parties prior to June 20, 2027, unless terminated earlier. The term of each work order terminates upon completion of the services under such work order, unless terminated earlier. We can terminate the WuXi Biologics MSA or any work order at any time upon 30 days' prior written notice and immediately upon written notice if WuXi Biologics fails to obtain or maintain required material governmental licenses or approvals. Either party may terminate a work order (i) at any time upon six months' prior notice with reasonable cause, provided however that if WuXi Biologics terminates a work order in such manner, no termination or cancellation fees shall be paid by us and (ii) immediately for cause upon (a) the other party's material breach that remains uncured for 30 days after notice of such breach, (b) the other party's bankruptcy or (c) a force majeure event that prevents performance for a period of at least 90 days.

Cell Line License Agreement

In April 2023, Paragon and WuXi Biologics entered into the Cell Line License Agreement, which was subsequently novated to us by Paragon pursuant to the Novation Agreement. Under the Cell Line License Agreement, we received a non-exclusive, worldwide, sublicensable license to certain of WuXi Biologics's know-how, cell line, biological materials (the "WuXi Biologics Licensed Technology") and media and feeds to make, have made, use, sell and import certain therapeutic products produced through the use of the cell line licensed by WuXi Biologics under the Cell Line License Agreement (the "WuXi Biologics Licensed Products"). Specifically, the WuXi Biologics Licensed Technology is used in certain manufacturing activities in support of the SPY001 program.

In consideration for the license, we agreed to pay WuXi Biologics a non-refundable license fee of $150,000. Additionally, if we manufacture all of our commercial supplies of bulk drug product with a manufacturer other than WuXi Biologics or its affiliates, we are required to make royalty payments to WuXi Biologics in an amount equal to a less than one percent of global net sales of WuXi Biologics Licensed Products manufactured by a third-party manufacturer (the "Royalty"). If we manufacture part of our commercial supplies of the WuXi Biologics Licensed Products with WuXi Biologics or its affiliates, then the Royalty will be reduced accordingly on a pro rata basis.

The Cell Line License Agreement will continue indefinitely unless terminated (i) by us upon six months' prior written notice and our payment of all undisputed amounts due to WuXi Biologics through the effective date of termination, (ii) by WuXi Biologics for a material breach by us that remains uncured for 60 days after written notice, (iii) by WuXi Biologics if we fail to make a payment and such failure continues for 30 days after receiving notice of such failure, or (iv) by either party upon the other party's bankruptcy.

Paragon Agreement

In May 2023, Pre-Merger Spyre entered into the Paragon Agreement with Paragon and Parapyre. Pursuant to the Paragon Agreement, the Option provided for the right to acquire the intellectual property rights related to four research programs from Paragon in accordance with a license agreement to be entered into following each exercise of the Option. Under the Paragon Agreement, the terms of such license agreement would be consistent with the economics and other terms set out in the Paragon Agreement and, in the event of failure to reach an agreement on the definitive terms, the matter would be resolved via arbitration. In consideration for the Option granted under the Paragon Agreement, Pre-Merger Spyre was obligated to pay Paragon an upfront cash amount of $3.0 million in research initiation fees. In addition, Pre-Merger Spyre was obligated to compensate Paragon on a quarterly basis for its services performed under each research program based on the actual costs incurred with mark-up costs pursuant to the terms of the Paragon Agreement. As of the date of the Asset Acquisition, Pre-Merger Spyre had incurred total expenses of $19.0 million under the Paragon Agreement since inception, which included the $3.0 million research initiation fee and $16.0 million of historical reimbursable expenses owed to Paragon. As of June 22, 2023, $19.0 million was unpaid and was assumed by us through the Asset Acquisition.

As a result of the Asset Acquisition, we assumed the rights and obligations of Pre-Merger Spyre under the Paragon Agreement, including the Parapyre Option Obligation. Pursuant to the Paragon Agreement, on a research program-by-research program basis following the finalization of the research plan for each respective research program, we are required to pay Paragon a nonrefundable fee in cash of $0.8 million.

On July 12, 2023 and December 14, 2023, we exercised our Option available under the Paragon Agreement with respect to the SPY001 and SPY002 research programs, respectively, and expect to enter into the SPY001 License Agreement and the SPY002 License Agreement. Our Option available under the Paragon Agreement with respect to the SPY003 and SPY004 programs remains unexercised.

Following the execution of each of the SPY001 License Agreement and SPY002 License Agreement, we will be obligated to pay Paragon up to $22.0 million upon the achievement of specific development, regulatory and clinical milestones for the first product under each agreement, respectively, that achieves such specified milestones. Upon execution of each of the SPY001 License Agreement and the SPY002 License Agreement, we expect to pay Paragon a $1.5 million fee for nomination of a development candidate, as applicable, and we expect to be obligated to make a further milestone payment of $2.5 million upon the first dosing of a human patient in a Phase 1 trial. Subject to the execution of the Option with respect to the SPY003 or SPY004 research programs, we expect to be obligated to make similar payments upon and following the execution of license agreements with respect to these research programs, respectively.

Competition

We expect to face intense competition from other biopharmaceutical companies that are developing agents for the treatment of inflammatory diseases. If approved for the treatment of patients with moderate-to-severe IBD, our portfolio of products would compete with TNF antibodies including Humira (AbbVie), Remicade (Johnson & Johnson), and Simponi (Johnson & Johnson); Omvoh (Lilly) IL-12/23 and IL-23 antibodies including Stelara (Johnson & Johnson) and Skyrizi (AbbVie); α4ß7 antibody Entyvio (Takeda); JAK inhibitors including Xeljanz (Pfizer), Rinvoq (AbbVie); and S1P1 receptor modulating therapies including Zeposia (Bristol Myers Squibb) and Velsipity (Pfizer).

We are aware of several companies with product candidates in development for the treatment of patients with IBD, including Merck's MK-7240, Roche/Roivant's RVT-3101, and Sanofi/Teva's TEV-48574 TL1A antibodies; additional IL-23/IL-23Rs including Tremfya and JNJ-2113 (Johnson & Johnson); and oral anti- integrin agents including Morphic Therapeutic's MORF-057, and Gilead's GS-1427, and a discovery program at Dice Therapeutics (Lilly).

Government Regulation

The FDA and other regulatory authorities at federal, state and local levels, as well as in foreign countries, extensively regulate, among other things, the research, development, testing, manufacture, quality control, import, export, safety, effectiveness, labeling, packaging, storage, distribution, record keeping, approval, advertising, promotion, marketing, post-approval monitoring and post-approval reporting of biologics such as those we are developing. We, along with our third-party contractors, will be required to navigate the various preclinical, clinical and commercial approval requirements of the governing regulatory agencies of the countries in which we wish to conduct studies or seek approval or licensure of our product candidates.

United States Biologics Regulation

In the United States, biological products are subject to regulation under the Federal Food, Drug, and Cosmetic Act ("FDCA"), the Public Health Service Act ("PHSA") and other federal, state, local, and foreign statutes and regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, and local statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or following approval may subject an applicant to administrative action and judicial sanctions. The process required by the FDA before biologic product candidates may be marketed in the United States generally involves the following:

- completion of preclinical laboratory tests and animal studies performed in accordance with the FDA's current Good Laboratory Practices ("GLP") regulation;
- submission to the FDA of an investigational new drug application ("IND"), which must become effective before clinical trials may begin and must be updated annually or when significant changes are made;
- approval by an independent institutional review board ("IRB"), or ethics committee at each clinical site before the trial is commenced;

- manufacture of the proposed biologic candidate in accordance with current Good Manufacturing Practices (“cGMPs”);
- performance of adequate and well-controlled human clinical trials in accordance with current Good Clinical Practice (“GCP”) requirements to establish the safety, purity and potency of the proposed biologic product candidate for its intended purpose;
- preparation of and submission to the FDA of a Biologics License Application ("BLA"), after completion of all pivotal clinical trials;
- satisfactory completion of an FDA Advisory Committee review, if applicable;
- a determination by the FDA within 60 days of its receipt of a BLA to file the application for review;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities at which the proposed product is produced to assess compliance with cGMPs, and to assure that the facilities, methods and controls are adequate to preserve the biological product’s continued safety, purity and potency, and of selected clinical investigation sites to assess compliance with GCPs; and
- FDA review and approval of a BLA to permit commercial marketing of the product for particular indications for use in the United States.

Preclinical and Clinical Development

Prior to beginning any clinical trial with a product candidate, in the United States, we must submit an IND to the FDA. An IND is a request for authorization from the FDA to administer an investigational new drug product to humans. The central focus of an IND submission is on the general investigational plan and the protocol or protocols for preclinical studies and clinical trials. The IND also includes results of animal and in vitro studies assessing the toxicology, pharmacokinetics, pharmacology and pharmacodynamic characteristics of the product, chemistry, manufacturing and controls information, and any available human data or literature to support the use of the investigational product. An IND must become effective before human clinical trials may begin. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day period, raises safety concerns or questions about the proposed clinical trial. In such a case, the IND may be placed on clinical hold and the IND sponsor and the FDA must resolve any outstanding concerns or questions before the clinical trial can begin. Submission of an IND therefore may or may not result in FDA authorization to begin a clinical trial.

In addition to the IND submission process, supervision of human gene transfer trials includes evaluation and assessment by an institutional biosafety committee (“IBC”), a local institutional committee that reviews and oversees research utilizing recombinant or synthetic nucleic acid molecules at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment and such review may result in some delay before initiation of a clinical trial.

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical study. Clinical trials are conducted under protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A separate submission to the existing IND must be made for each successive clinical trial conducted during product development and for any subsequent protocol amendments. Furthermore, an independent IRB for each site proposing to conduct the clinical trial must review and approve the plan for any clinical trial and its informed consent form before the clinical trial begins at that site, and must monitor the study until completed.

Regulatory authorities, the IRB or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects are being exposed to an unacceptable health risk or that the trial is unlikely to meet its stated objectives. Some studies also include oversight by an independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board, which provides authorization for whether or not a study may move forward at designated check points based on access to certain data from the study and may halt the clinical trial if it determines that there is an unacceptable safety risk for subjects or other grounds, such as no demonstration of efficacy. There are also requirements governing the reporting of ongoing preclinical studies and clinical trials and clinical study results to public registries.

For purposes of BLA approval, human clinical trials are typically conducted in three sequential phases that may overlap.

- Phase 1. The investigational product is initially introduced into healthy human subjects or patients with the target disease or condition. These studies are designed to test the safety, dosage tolerance, absorption, metabolism and distribution of the investigational product in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness.

- Phase 2. The investigational product is administered to a limited patient population with a specified disease or condition to evaluate the preliminary efficacy, optimal dosages and dosing schedule and to identify possible adverse side effects and safety risks. Multiple Phase 2 clinical trials may be conducted to obtain information prior to beginning larger and more expensive Phase 3 clinical trials.

- Phase 3. The investigational product is administered to an expanded patient population to further evaluate dosage, to provide statistically significant evidence of clinical efficacy and to further test for safety, generally at multiple geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk/benefit ratio of the investigational product and to provide an adequate basis for product approval.

In some cases, the FDA may require, or companies may voluntarily pursue, additional clinical trials after a product is approved to gain more information about the product. These so-called Phase 4 studies may be made a condition to approval of the BLA. Concurrent with clinical trials, companies may complete additional animal studies and develop additional information about the biological characteristics of the product candidate and must finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, must develop methods for testing the identity, strength, quality and purity of the final product, or for biologics, the safety, purity and potency. Additionally, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

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 IND requirements must be met unless waived. When the foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with certain FDA regulatory requirements in order to use the study as support for an IND or application for marketing approval or licensure, including that the study was conducted in accordance with GCP, including review and approval by an independent ethics committee and use of proper procedures for obtaining informed consent from subjects, and the FDA is able to validate the data from the study through an onsite inspection if the FDA deems such inspection necessary. The GCP requirements encompass both ethical and data integrity standards for clinical studies.

BLA Submission and Review

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, the results of product development, nonclinical studies and clinical trials are submitted to the FDA as part of a BLA requesting approval to market the product for one or more indications. The BLA must include all relevant data available from pertinent preclinical studies 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 studies intended to test the safety and effectiveness of the product, or from a number of alternative sources, including studies initiated and sponsored by investigators. The submission of a BLA requires payment of a substantial application user fee to the FDA, unless a waiver or exemption applies.

In addition, under the Pediatric Research Equity Act ("PREA"), a BLA or supplement to a BLA must contain data to assess the safety and effectiveness of the biological product candidate 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. The Food and Drug Administration Safety and Innovation Act requires that a sponsor who is planning to submit a marketing application for a biological product that includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration submit an initial pediatric study plan ("PSP") within sixty days after an end-of-Phase 2 meeting or as may be agreed between the sponsor and FDA. Unless otherwise required by regulation, PREA does not apply to any biological product for an indication for which orphan designation has been granted.

Within 60 days following submission of the application, the FDA reviews a BLA submitted to determine if it is substantially complete before the agency accepts it for filing. The FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission and may request additional information.

In this event, the BLA must be resubmitted with the additional information. Once a BLA has been accepted for filing, the FDA's goal is to review standard applications within ten months after the filing date, or, if the application qualifies for priority review, six months after the FDA accepts the application for filing. In both standard and priority reviews, the review process may also be extended by FDA requests for additional information or clarification. The FDA reviews a BLA to determine, among other things, whether a product is safe, pure and potent and the facility in which it is manufactured, processed, packed or held meets standards designed to assure the product's continued safety, purity and potency. The FDA may convene an advisory committee to provide clinical insight on application review questions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving a BLA, the FDA will typically inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with GMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure compliance with cGCPs. If the FDA determines that the application, manufacturing process or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and often will request additional testing or information. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

After the FDA evaluates a BLA and conducts inspections of manufacturing facilities where the investigational product and/or its drug substance will be produced, 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 will describe all of the deficiencies that the FDA has identified in the BLA, except that where the FDA determines that the data supporting the application are inadequate to support approval, the FDA may issue the Complete Response letter without first conducting required inspections, testing submitted product lots and/or reviewing proposed labeling. In issuing the Complete Response letter, the FDA may recommend actions that the applicant might take to place the BLA in condition for approval, including requests for additional information or clarification. The FDA may delay or refuse approval of a BLA if applicable regulatory criteria are not satisfied, require additional testing or information and/or require post-marketing testing and surveillance to monitor safety or efficacy of a product.

If regulatory approval of a product is granted, such approval will be granted for particular indications and may entail limitations on the indicated uses for which such product may be marketed. For example, the FDA may approve the BLA with a Risk Evaluation and Mitigation Strategy ("REMS") to ensure the benefits of the product outweigh its risks. A REMS is a safety strategy to manage a known or potential serious risk associated with a product and to enable patients to have continued access to such medicines by managing their safe use, and could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. The FDA also may condition approval on, among other things, changes to proposed labeling or the development of adequate controls and specifications. Once approved, the FDA may withdraw the product approval if compliance with pre- and post-marketing requirements is not maintained or if problems occur after the product reaches the marketplace. The FDA may require one or more Phase 4 post-market studies and surveillance to further assess and monitor the product's safety and effectiveness after commercialization, and may limit further marketing of the product based on the results of these post-marketing studies.

Expedited Development and Review Programs

The FDA offers a number of expedited development and review programs for qualifying product candidates. The fast track program is intended to expedite or facilitate the process for reviewing new products that meet certain criteria. Specifically, new products are eligible for fast track designation if they are intended to treat a serious or life-threatening disease or condition and data demonstrate the potential to address unmet medical needs for the disease or condition. Fast track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a fast track product has opportunities for more frequent interactions with the review team during product development and, once a BLA is submitted, the product may be eligible for priority review. A fast track product may also be eligible for rolling review, where the FDA may consider for review sections of the BLA on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the BLA, the FDA agrees to accept sections of the BLA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the BLA.

A product intended to treat a serious or life-threatening disease or condition may also be eligible for breakthrough therapy designation to expedite its development and review. A product can receive breakthrough therapy designation if preliminary clinical evidence indicates that the product, alone or in combination with one or more other drugs or biologics, may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The designation includes all of the fast track program features, as well as more intensive FDA interaction and guidance beginning as early as Phase 1 and an organizational commitment to expedite the development and review of the product, including involvement of senior managers.

Any marketing application for a biologic submitted to the FDA for approval, including a product with a fast track designation and/or breakthrough therapy designation, may be eligible for other types of FDA programs intended to expedite the FDA review and approval process, such as priority review and accelerated approval. A product is eligible for priority review if there is evidence it has the potential to provide a significant improvement in the treatment, diagnosis or prevention of a serious disease or condition. For original BLAs, priority review designation means the FDA's goal is to take action on the marketing application within six months of the 60-day filing date (as compared to ten months under standard review).

Additionally, products studied for their safety and effectiveness in treating serious or life-threatening diseases or conditions may receive accelerated approval upon a determination that the product has 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, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. As a condition of accelerated approval, the FDA will generally require the sponsor to perform adequate and well-controlled post-marketing clinical studies to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit. Under the Food and Drug Omnibus Reform Act of 2022 the FDA may require, as appropriate, that such studies be underway prior to approval or within a specific time period after the date of approval for a product granted accelerated approval. Products receiving accelerated approval may be subject to expedited withdrawal procedures if the sponsor fails to conduct the required post-marketing studies or if such studies fail to verify the predicted clinical benefit. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product.

Fast track designation, breakthrough therapy designation and priority review do not change the standards for approval but may expedite the development or approval process. Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

Combination Therapy

Combination therapy is a treatment modality that involves the use of two or more drugs to be used in combination to treat a disease or condition. If those drugs are combined in one dosage form, such as one pill, that is known as a fixed dose combination product and it is reviewed pursuant to the FDA's Combination Rule at 21 CFR 300.50. The rule provides that two or more drugs may be combined in a single dosage form when each component contributes to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.

But not all combination therapy falls under the category of a fixed dose combination. For example, the FDA recognizes that two drugs in separate dosage forms and in separate packaging, that otherwise might be administered as monotherapy for an indication, also may be used in combination for the same indication. In 2013, the FDA issued guidance to assist sponsors that were developing the range of combination therapies that fall outside the category of fixed dose combinations. That guidance provides recommendations and advice on such topics as: (1) assessment at the outset whether two or more therapies are appropriate for use in combination; (2) guiding principles for nonclinical and clinical development of the combination; (3) options for regulatory pathways to seek marketing approval of the combination; and (4) post-marketing safety monitoring and reporting obligations. Given the wide range of potential combination therapy variations, the FDA indicated it intends to assess each potential combination on a case-by case basis and encouraged sponsors to engage in

early and regular consultation with the relevant review division at the agency throughout the development process for its proposed combination.

Regulation of Combination Products

Certain therapeutic products are comprised of multiple components, such as drug components and device components, that would normally be subject to different regulatory frameworks by the FDA and frequently regulated by different centers at the FDA. These products are known as combination products. Under the FDCA, the FDA is charged with assigning a center with primary jurisdiction, or a lead center, for review of a combination product. The determination of which center will be the lead center is based on the "primary mode of action" of the combination product. Thus, if the primary mode of action of a drug-device combination product is attributable to the drug product, the FDA center responsible for premarket review of the drug product would have primary jurisdiction for the combination product. The FDA has also established the Office of Combination Products to address issues surrounding combination products and provide more certainty to the regulatory review process. That office serves as a focal point for combination product issues for agency reviewers and industry. It is also responsible for developing guidance and regulations to clarify the regulation of combination products, and for assignment of the FDA center that has primary jurisdiction for review of combination products where the jurisdiction is unclear or in dispute. A combination product with a primary mode of action attributable to the drug or biologic component generally would be reviewed and approved pursuant to the drug or biologic approval processes set forth in the FDCA. In reviewing the NDA or BLA for such a product, however, FDA reviewers would consult with their counterparts in the FDA's Center for Devices and Radiological Health to ensure that the device component of the combination product met applicable requirements regarding safety, effectiveness, durability and performance. In addition, under FDA regulations, combination products are subject to cGMP requirements applicable to both drugs and devices, including the Quality System Regulation applicable to medical devices.

Complementary Diagnostics

The success of our product candidates may depend, in part, on the development and commercialization of a complementary diagnostic. Complementary diagnostics can identify patients who are most likely to benefit from a particular therapeutic product; identify patients likely to be at increased risk for serious side effects as a result of treatment with a particular therapeutic product; or monitor response to treatment with a particular therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness. Complementary diagnostics are regulated as medical devices by the FDA. The level of risk associated with a new diagnostic test combined with available controls to mitigate risk determines whether a complementary diagnostic device requires Premarket Approval ("PMA") from the FDA or if it can be cleared by the agency through the 510(k) premarket notification process based on a showing of substantial equivalence to a commercially available device. The use of the complementary diagnostic device will be stipulated in the labeling of the therapeutic product, and vice versa.

Post-Approval Requirements

Any products manufactured or distributed by us pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to record-keeping, reporting of adverse experiences, periodic reporting, product sampling and distribution, and advertising and promotion of the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing user fee requirements, under which the FDA assesses an annual program fee for each product identified in an approved BLA. Biologic manufacturers and their subcontractors 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 cGMPs, which impose certain procedural and documentation requirements upon us and our third-party manufacturers. Changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMPs and impose reporting requirements upon us and any third-party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMPs and other aspects of regulatory compliance.

The FDA may withdraw approval if compliance with regulatory requirements and standards 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, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical studies to assess new safety risks; or imposition of distribution restrictions or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of a product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical studies;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of existing product approvals;
- product seizure or detention, or refusal of the FDA to permit the import or export of products;
- consent decrees, corporate integrity agreements, debarment or exclusion from federal healthcare programs;
- mandated modification of promotional materials and labeling and the issuance of corrective information;
- the issuance of safety alerts, Dear Healthcare Provider letters, press releases and other communications containing warnings or other safety information about the product; or
- injunctions or the imposition of civil or criminal penalties.

The FDA closely regulates the marketing, labeling, advertising and promotion of biologics. A company can make only those claims relating to safety and efficacy, purity and potency that are approved by the FDA and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. Failure to comply with these requirements can result in, among other things, adverse publicity, warning letters, corrective advertising and potential civil and criminal penalties. Physicians may prescribe legally available products for uses that are not described in the product's labeling and that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, restrict manufacturer's communications on the subject of off-label use of their products.

Biosimilars and Reference Product Exclusivity

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act (collectively, the "ACA"), includes a subtitle called the Biologics Price Competition and Innovation Act of 2009 ("BPCIA"), which created an abbreviated approval pathway for biological products that are highly similar, or "biosimilar," to or interchangeable with an FDA-approved reference biological product. The FDA has issued several guidance documents outlining an approach to review and approval of biosimilars.

Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, is generally shown through analytical studies, animal studies, and a clinical study or studies. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product in any given patient and, for products that are administered multiple times to an individual, the biologic and the reference biologic may be alternated or switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. A product shown to be biosimilar or interchangeable with an FDA-approved reference biological product may rely in part on the FDA's previous determination of safety and effectiveness for the reference product for approval, which can potentially reduce the cost and time required to obtain approval to market the product. Complexities associated with the larger, and often more complex, structures of biological products, as well as the processes by which such products are manufactured, pose significant hurdles to implementation of the abbreviated approval pathway that are still being worked out by the FDA. In September 2021, the FDA issued two guidance documents intended to inform prospective applicants and facilitate the development of proposed biosimilars and interchangeable biosimilars, as well as to describe the FDA's interpretation of certain statutory requirements added by the BPCIA.

Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date that the reference product was first licensed by the FDA. In addition, the approval of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference

product was first licensed. During this 12-year period of exclusivity, another company may still market a competing version of the reference product if the FDA approves a full BLA for the competing product containing that applicant's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of its product. The BPCIA also created certain exclusivity periods for biosimilars approved as interchangeable products. At this juncture, it is unclear whether products deemed "interchangeable" by the FDA will, in fact, be readily substituted by pharmacies, which are governed by state pharmacy law.

A reference biologic is granted twelve years of exclusivity from the time of first licensure of the reference product. The first biologic product submitted under the abbreviated approval pathway that is determined to be interchangeable with the reference product has exclusivity against other biologics submitted under the abbreviated approval pathway for the lesser of (i) one year after the first commercial marketing, (ii) 18 months after approval if there is no legal challenge, (iii) 18 months after the resolution in the applicant's favor of a lawsuit challenging the biologics' patents if an application has been submitted, or (iv) 42 months after the application has been approved if a lawsuit is ongoing within the 42-month period.

A biological product can also obtain pediatric market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric study in accordance with an FDA-issued "Written Request" for such a study.

The BPCIA is complex and continues to be interpreted and implemented by the FDA. In July 2018, the FDA announced an action plan to encourage the development and efficient review of biosimilars, including the establishment of a new office within the agency that will focus on therapeutic biologics and biosimilars. On December 20, 2020, Congress amended the PHSA as part of the COVID-19 relief bill to further simplify the biosimilar review process by making it optional to show that conditions of use proposed in labeling have been previously approved for the reference product, which used to be a requirement of the application. In addition, government proposals have sought to reduce the 12-year reference product exclusivity period. Other aspects of the BPCIA, some of which may impact the BPCIA exclusivity provisions, have also been the subject of recent litigation. As a result, the ultimate impact, implementation, and impact of the BPCIA is subject to significant uncertainty.

As discussed below, the Inflation Reduction Act of 2022 ("IRA") is a significant new law that intends to foster generic and biosimilar competition and to lower drug and biologic costs.

Other Healthcare Laws and Compliance Requirements

Pharmaceutical companies are subject to additional healthcare regulation and enforcement by the federal government and by authorities in the states and foreign jurisdictions in which they conduct their business. Such laws include, without limitation: the federal Anti-Kickback Statute ("AKS"); the federal False Claims Act ("FCA"); the Health Insurance Portability and Accountability Act of 1996 ("HIPAA") and similar foreign, federal and state fraud, abuse and transparency laws.

The AKS prohibits, among other things, persons and entities from knowingly and willfully soliciting, receiving, offering or paying remuneration, to induce, or in return for, either the referral of an individual, or the purchase or recommendation of an item or service for which payment may be made under any federal healthcare program. The term remuneration has been interpreted broadly to include anything of value. The AKS has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand, and prescribers and purchasers on the other. The government often takes the position that to violate the AKS, only one purpose of the remuneration need be to induce referrals, even if there are other legitimate purposes for the remuneration. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from AKS prosecution, but they are drawn narrowly and practices that involve remuneration, such as consulting agreements, that may be alleged to be intended to induce prescribing, purchasing or recommending may be subject to scrutiny if they do not qualify for an exception or safe harbor. Our practices may not in all cases meet all of the criteria for protection under a statutory exception or regulatory safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the AKS. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all of its facts and circumstances. 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.

Civil and criminal false claims laws, including the FCA, and civil monetary penalty laws, which can be enforced through civil whistleblower or qui tam actions, prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment of federal government funds, including in federal healthcare programs, that are false or fraudulent. Pharmaceutical and other healthcare companies have been prosecuted under these laws for engaging in a variety of different types of conduct that "caused" the submission of false claims to federal healthcare programs. Under the AKS, for example, a claim resulting from a violation of the AKS is deemed to be a false or fraudulent claim for purposes of the FCA.

HIPAA created additional federal criminal statutes that prohibit, among other things, executing a scheme to defraud any healthcare benefit program, including private third-party payors, and making false statements relating to healthcare matters. A person or entity does not need to have actual knowledge of the healthcare fraud statute implemented under HIPAA or specific intent to violate the statute in order to have committed a violation.

The FDCA addresses, among other things, the design, production, labeling, promotion, manufacturing, and testing of drugs, biologics and medical devices, and prohibits such acts as the introduction into interstate commerce of adulterated or misbranded drugs or devices. The PHSA also prohibits the introduction into interstate commerce of unlicensed or mislabeled biological products.

The U.S. federal Physician Payments Sunshine Act requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to annually report to the Centers for Medicaid & Medicare Services ("CMS") information related to payments or other transfers of value to various healthcare professionals including physicians, physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, certified nurse-midwives, and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Beginning on January 1, 2023, California Assembly Bill 1278 requires California physicians and surgeons to notify patients of the Open Payments database established under the federal Physician Payments Sunshine Act.

We are also subject to additional similar U.S. state and foreign law equivalents of each of the above federal laws, which, in some cases, differ from each other in significant ways, and may not have the same effect, thus complicating compliance efforts. If our operations are found to be in violation of any of such laws or any other governmental regulations that apply, we may be subject to penalties, including, without limitation, civil, criminal and administrative penalties, damages, fines, exclusion from government-funded healthcare programs, such as Medicare and Medicaid or similar programs in other countries or jurisdictions, integrity oversight and reporting obligations to resolve allegations of non-compliance, disgorgement, individual imprisonment, contractual damages, reputational harm, diminished profits and the curtailment or restructuring of our operations.

Data Privacy and Security

Numerous state, federal, and foreign laws govern the collection, dissemination, use, access to, confidentiality, and security of personal information, including health-related information. In the United States, numerous federal and state laws and regulations, including state data breach notification laws, state health information privacy laws, and federal and state consumer protection laws and regulations, govern the collection, use, disclosure, and protection of health-related and other personal information could apply to our operations or the operations of our partners. For example, HIPAA, as amended by the Health Information Technology for Economic and Clinical Health ("HITECH"), and their respective implementing regulations imposes data privacy, security, and breach notification obligations on certain health care providers, health plans, and health care clearinghouses, known as covered entities, as well as their business associates and their covered subcontractors that perform certain services that involve using, disclosing, creating, receiving, maintaining, or transmitting individually identifiable protected health information ("PHI") for or on behalf of such covered entities. These requirements imposed by HIPAA and the HITECH Act on covered entities and business associates include entering into agreements that require business associates protect PHI provided by the covered entity against improper use or disclosure, among other things; following certain standards for the privacy of PHI, which limit the disclosure of a patient's past, present, or future physical or mental health or condition or information about a patient's receipt of health care if the information identifies, or could reasonably be used to identify, the individual; ensuring the confidentiality, integrity, and availability of all PHI created, received, maintained, or transmitted in electronic form, to identify and protect against reasonably anticipated threats or impermissible uses or disclosures to the security and integrity of such PHI; and reporting of breaches of PHI to individuals and regulators. Entities that are found to be in violation of HIPAA may be subject to significant civil, criminal, and administrative fines and penalties and/or additional reporting and oversight obligations if required to enter into a

resolution agreement and corrective action plan with the U.S. Department of Health and Human Services ("HHS") to settle allegations of HIPAA non-compliance. A covered entity or business associate is also liable for civil money penalties for a violation that is based on an act or omission of any of its agents, which may include a downstream business associate, as determined according to the federal common law of agency. HITECH also increased the civil and criminal penalties applicable to covered entities and business associates and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce HIPAA and seek attorneys' fees and costs associated with pursuing federal civil actions. To the extent that we submit electronic healthcare claims and payment transactions that do not comply with the electronic data transmission standards established under HIPAA and HITECH, payments to us may be delayed or denied.

Even when HIPAA does not apply, according to the FTC, violating consumers' privacy rights or failing to take appropriate steps to keep consumers' personal information secure may constitute unfair acts or practices in or affecting commerce in violation of Section 5(a) of the Federal Trade Commission Act.

In addition, certain state laws, such as the California Consumer Privacy Act of 2018 ("CCPA"), as amended by the California Privacy Rights Act of 2020 ("CPRA"), govern the privacy and security of personal information, including health-related information in certain circumstances, some of which are more stringent than HIPAA and many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. The CCPA/CPRA applies to personal data of consumers, business representatives, and employees, and imposes obligations on certain businesses that do business in California, including to provide specific disclosures in privacy notices, rights to California residents in relation to their personal information. Health information falls under the CCPA/CPRA's definition of personal information where it identifies, relates to, describes, or is reasonably capable of being associated with or could reasonably be linked with a particular consumer or household — unless it is subject to HIPAA — and is included under a new category of personal information, "sensitive personal information," which is offered greater protection. Failure to comply with these laws, where applicable, can result in the imposition of significant civil and/or criminal penalties and private litigation. Privacy and security laws, regulations, and other obligations are constantly evolving, may conflict with each other to complicate compliance efforts, and can result in investigations, proceedings, or actions that lead to significant civil and/or criminal penalties and restrictions on data processing. Additionally, our use of artificial intelligence and machine learning may be subject to laws and evolving regulations regarding the use of artificial intelligence/machine learning, controlling for data bias, and antidiscrimination.

In addition, the CPRA expands the CCPA's requirements, including by adding a new right for individuals to correct their personal information and establishing a new regulatory agency to implement and enforce the law. Other states, such as Virginia, Colorado, Connecticut and Utah, have also passed comprehensive privacy laws, and similar laws are being considered in several other states, as well as at the federal and local levels. While the laws in these states, like the CCPA, also exempt some data processed in the context of clinical trials, such developments further complicate compliance efforts, and increase legal risk and compliance costs for us and the third parties upon whom we rely.

Coverage and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any pharmaceutical or biological product for which we obtain regulatory approval. Sales of any product, if approved, depend, in part, on the extent to which such product will be covered by third-party payors, such as federal, state, and foreign government healthcare programs, commercial insurance and managed healthcare organizations, and the level of reimbursement, if any, for such product by third-party payors. Decisions regarding whether to cover any of our product candidates, if approved, the extent of coverage and amount of reimbursement to be provided are made on a plan-by-plan basis. Further, no uniform policy for coverage and reimbursement exists in the United States, and coverage and reimbursement can differ significantly from payor to payor. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement rates, but also have their own methods and approval process apart from Medicare determinations. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our product candidates to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

Third-party payors are increasingly challenging the prices charged for medical products and services, examining the medical necessity and reviewing the cost effectiveness of pharmaceutical or biological products, medical devices and medical services, in addition to questioning safety and efficacy. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit sales of any product that receives approval. Decreases in third-party

reimbursement for any product or a decision by a third-party not to cover a product could reduce physician usage and patient demand for the product.

For products administered under the supervision of a physician, obtaining coverage and adequate reimbursement may be particularly difficult because of the higher prices often associated with such drugs. Additionally, separate reimbursement for the product itself or the treatment or procedure in which the product is used may not be available, which may impact physician utilization. In addition, companion diagnostic tests require coverage and reimbursement separate and apart from the coverage and reimbursement for their companion pharmaceutical or biological products. Similar challenges to obtaining coverage and reimbursement, applicable to pharmaceutical or biological products, will apply to companion diagnostics.

In addition, the U.S. government, state legislatures and foreign governments have continued implementing cost- containment programs, including price controls, restrictions on coverage and reimbursement and requirements for substitution of generic products. The IRA provides CMS with significant new authorities intended to curb drug costs and to encourage market competition. For the first time, CMS will be able to directly negotiate prescription drug prices and to cap out-of-pocket costs. Each year, CMS will select and negotiate a preset number of high-spend drugs and biologics that are covered under Medicare Part B and Part D that do not have generic or biosimilar competition. On August 29, 2023, HHS announced the list of the first ten drugs that will be subject to price negotiations. These price negotiations will begin in 2023, although the Medicare drug price negotiation program is currently subject to legal challenges. The IRA also provides a new “inflation rebate” covering Medicare patients that took effect in 2023 and is intended to counter certain price increases in prescriptions drugs. The inflation rebate provision will require drug manufacturers to pay a rebate to the federal government if the price for a drug or biologic under Medicare Part B and Part D increases faster than the rate of inflation. To support biosimilar competition, beginning in October 2022, qualifying biosimilars may receive a Medicare Part B payment increase for a period of five years. Separately, if a biologic drug for which no biosimilar exists delays a biosimilar’s market entry beyond two years, CMS will be authorized to subject the biologics manufacturer to price negotiations intended to ensure fair competition. Notwithstanding these provisions, the IRA’s impact on commercialization and competition remains largely uncertain.

Healthcare Reform

The United States and some foreign jurisdictions are considering or have enacted a number of reform proposals to change the healthcare system. There is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by federal and state legislative initiatives, including those designed to limit the pricing, coverage, and reimbursement of pharmaceutical and biopharmaceutical products, especially under government-funded health care programs, and increased governmental control of drug pricing.

The ACA, which was enacted in March 2010, substantially changed the way healthcare is financed by both governmental and private insurers in the United States, and significantly affected the pharmaceutical industry. The ACA contains a number of provisions of particular import to the pharmaceutical and biotechnology industries, including, but not limited to, those governing enrollment in federal healthcare programs, a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, and annual fees based on pharmaceutical companies’ share of sales to federal health care programs. Since its enactment, there have been judicial and Congressional challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. For example, the IRA, among other things, extends enhanced subsidies for individuals purchasing health insurance coverage in ACA marketplaces through plan year 2025. The IRA also eliminates the “donut hole” under the Medicare Part D program beginning in 2025 by significantly lowering the beneficiary maximum out-of-pocket cost and creating a new manufacturer discount program.

Other legislative changes have been proposed and adopted since the ACA was enacted, including automatic aggregate reductions of Medicare payments to providers of on average 2% per fiscal year as part of the federal budget sequestration under the Budget Control Act of 2011. These reductions went into effect in April 2013 and, due to subsequent legislative amendments, will remain in effect until 2032 unless additional action is taken by Congress.

In addition, the Bipartisan Budget Act of 2018, among other things, amended the Medicare Act (as amended by the ACA) to increase the point-of-sale discounts that manufacturers must agree to offer under the Medicare Part D coverage discount program from 50% to 70% off negotiated prices of applicable brand drugs to

eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs being covered under Medicare Part D.

Moreover, there has recently been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed and enacted federal and state measures designed to, among other things, reduce the cost of prescription drugs, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. For example, in May 2019, CMS adopted a final rule allowing Medicare Advantage Plans the option to use step therapy for Part B drugs, permitting Medicare Part D plans to apply certain utilization controls to new starts of five of the six protected class drugs, and requiring the Explanation of Benefits for Part D beneficiaries to disclose drug price increases and lower cost therapeutic alternatives, which went into effect on January 1, 2021. In response to the Biden administration's October 2022 executive order, on February 14, 2023, HHS released a report outlining three new models for testing by the CMS Innovation Center which will be evaluated on their ability to lower the cost of drugs, promote accessibility, and improve quality of care. It is unclear whether the models will be utilized in any health reform measures in the future. Further, on December 7, 2023, the Biden administration announced an initiative to control the price of prescription drugs through the use of march-in rights under the Bayh-Dole Act. On December 8, 2023, the National Institute of Standards and Technology published for comment a Draft Interagency Guidance Framework for Considering the Exercise of March-In Rights which for the first time includes the price of a product as one factor an agency can use when deciding to exercise march-in rights. While march-in rights have not previously been exercised, it is uncertain if that will continue under the new framework.

Notwithstanding the IRA, continued legislative and enforcement interest exists in the United States with respect to specialty drug pricing practices. Specifically, we expect regulators to continue pushing for transparency to drug pricing, reducing the cost of prescription drugs under Medicare, reviewing the relationship between pricing and manufacturer patient programs, and reforming government program reimbursement methodologies for drugs.

Other Government Regulation Outside of the United States

In addition to regulations in the United States, we are subject to a variety of regulations in other jurisdictions governing, among other things, research and development, clinical trials, testing, manufacturing, safety, efficacy, quality control, labeling, packaging, storage, record keeping, distribution, reporting, export and import, advertising, marketing and other promotional practices involving biological products as well as authorization, approval as well as post-approval monitoring and reporting of our products. Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials.

The requirements and process governing the conduct of clinical trials, including requirements to conduct additional clinical trials, product licensing, safety reporting, post-authorization requirements, marketing and promotion, interactions with healthcare professionals, pricing and reimbursement may vary widely from country to country. No action can be taken to market any product in a country until an appropriate approval application has been approved by the regulatory authorities in that country. The current approval process varies from country to country, and the time spent in gaining approval varies from that required for FDA approval. In certain countries, the sales price of a product must also be approved. The pricing review period often begins after market approval is granted. Even if a product is approved by a regulatory authority, satisfactory prices may not be approved for such product, which would make launch of such products commercially unfeasible in such countries.

Regulation in the European Union

European Data Laws

The collection and use of personal health data and other personal data in the European Union ("EU") is governed by the provisions of the European General Data Protection Regulation (EU) 2016/679 ("GDPR"), which came into force in May 2018, and related data protection laws in individual EU Member States. The GDPR imposes a number of strict obligations and restrictions on the ability to process, including collecting, analyzing and transferring, personal data of individuals, in particular with respect to health data from clinical

trials and adverse event reporting. The GDPR includes requirements relating to the legal basis of the processing (such as consent of the individuals to whom the personal data relates), the information provided to the individuals prior to processing their personal data, the notification obligations to the national data protection authorities, and the security and confidentiality of the personal data. EU Member States may also impose additional requirements in relation to health, genetic and biometric data through their national legislation.

In addition, the GDPR imposes specific restrictions on the transfer of personal data to countries outside of the European Economic Area ("EEA") that are not considered by the European Commission ("EC") to provide an adequate level of data protection. Appropriate safeguards are required to enable such transfers. Among the appropriate safeguards that can be used, the data exporter may use the standard contractual clauses ("SCCs"). With regard to the transfer of data from the EEA to the United States, on July 10, 2023, the EC adopted its adequacy decision for the EU-US Data Privacy Framework. On the basis of the new adequacy decision, personal data can flow from the EEA to U.S. companies participating in the framework.

Failure to comply with the requirements of the GDPR and the related national data protection laws of the EU Member States may result in significant monetary fines for noncompliance of up to €20 million or 4% of the annual global revenues of the noncompliant company, whichever is greater, other administrative penalties and a number of criminal offenses (punishable by uncapped fines) for organizations and, in certain cases, their directors and officers, as well as civil liability claims from individuals whose personal data was processed. Data protection authorities from the different EU Member States may still implement certain variations, enforce the GDPR and national data protection laws differently, and introduce additional national regulations and guidelines, which adds to the complexity of processing personal data in the EU. Guidance developed at both the EU level and at the national level in individual EU Member States concerning implementation and compliance practices are often updated or otherwise revised.

Furthermore, there is a growing trend towards the required public disclosure of clinical trial data in the EU, which adds to the complexity of obligations relating to processing health data from clinical trials. Such public disclosure obligations are provided in the new EU Clinical Trials Regulation No. 536/2014 (“CTR”), European Medical Agency ("EMA") disclosure initiatives and voluntary commitments by industry. Failure to comply with these obligations could lead to government enforcement actions and significant penalties against us, harm to our reputation, and adversely impact our business and operating results. The uncertainty regarding the interplay between different regulatory frameworks, such as the CTR and the GDPR, further adds to the complexity that we face with regard to data protection regulation.

With regard to the transfer of personal data from the EEA to the United Kingdom (“UK”), personal data may now freely flow from the EEA to the UK since the UK is deemed to have an adequate data protection level.

However, the adequacy decisions include a ‘sunset clause’ which entails that the decisions will automatically expire four years after their entry into force. Additionally, following the UK’s withdrawal from the EU and the EEA, companies also have to comply with the UK’s data protection laws (including the UK GDPR (as defined in section 3(10) (as supplemented by section 205(4)) of the Data Protection Act 2018 (the “DPA 2018”)), the DPA 2018, and related data protection laws in the UK). Separate from the fines that can be imposed by the GDPR, the UK regime has the ability to fine up to the greater of £17.5 million or 4% of global turnover.

Following the UK’s withdrawal from the EU and the EEA, companies are subject to specific transfer rules under the UK regime; personal data may flow freely from the UK to the EEA, since the EEA is deemed to have an adequate data protection level for purposes of the UK regime. These UK international transfer rules broadly mirror the GDPR rules. On February 2, 2022, the UK Secretary of State laid before the UK Parliament the international data transfer agreement (“IDTA”) and the international data transfer addendum to the EC’s standard contractual clauses for international data transfers (Addendum) and a document setting out transitional provisions. The IDTA and Addendum came into force on March 21, 2022 and replaced the old SCCs for the purposes of the UK regime. However, the transitional provisions, adopted with the IDTA and the Addendum, provide that contracts concluded on or before September 21, 2022 on the basis of any old SCCs continue to provide appropriate safeguards for the purpose of the UK regime until March 21, 2024, provided that the processing operations that are the subject matter of the contract remain unchanged and reliance on those clauses ensures that the transfer of personal data is subject to appropriate safeguards.

With regard to the transfer of personal data from the UK to the United States, the UK government has adopted an adequacy decision for the United States, the UK-US Data Bridge, which came into force on October 12, 2023. The UK-US Data Bridge recognizes the United States as offering an adequate level of data protection

where the transfer is to a U.S. company participating in the EU-US Data Privacy Framework and the UK Extension.

Drug and Biologic Development Process

Regardless of where they are conducted, all clinical trials included in applications for marketing authorization ("MA") for human medicines in the EU/EEA must have been carried out in accordance with EU regulations. This means that clinical trials conducted in the EU/EEA have to comply with EU clinical trial legislation but also that clinical trials conducted outside the EU/EEA have to comply with ethical principles equivalent to those set out in the EEA, including adhering to international good clinical practice and the Declaration of Helsinki. The conduct of clinical trials in the EU is governed by the CTR, which entered into force on January 31, 2022. The CTR replaced the Clinical Trials Directive 2001/20/EC, (“Clinical Trials Directive”) and introduced a complete overhaul of the existing regulation of clinical trials for medicinal products in the EU.

Under the former regime, which will expire after a transition period of three years as outlined below in more detail, before a clinical trial can be initiated it must be approved in each EU member state where there is a site at which the clinical trial is to be conducted. The approval must be obtained from two separate entities: the National Competent Authority ("NCA") and one or more Ethics Committees. NCA of the EU Member States in which the clinical trial will be conducted must authorize the conduct of the trial, and the independent Ethics Committee must grant a positive opinion in relation to the conduct of the clinical trial in the relevant EU member state before the commencement of the trial. Any substantial changes to the trial protocol or other information submitted with the clinical trial applications must be submitted to or approved by the relevant NCA and Ethics Committees. Under the current regime all suspected unexpected serious adverse reactions to the investigated drug that occur during the clinical trial must be reported to the NCA and to the Ethics Committees of the EU member state where they occur.

A more unified procedure will apply under the new CTR. A sponsor will be able to submit a single application for approval of a clinical trial through a centralized EU clinical trials portal (the "CTIS”). One national regulatory authority (the reporting EU member state proposed by the applicant) will take the lead in validating and evaluating the application and consult and coordinate with the other concerned EU Member States. If an application is rejected, it may be amended and resubmitted through the EU clinical trials portal. If an approval is issued, the sponsor may start the clinical trial in all concerned EU Member States. However, a concerned EU member state may in limited circumstances declare an “opt-out” from an approval and prevent the clinical trial from being conducted in such member state. The CTR also aims to streamline and simplify the rules on safety reporting, and introduces enhanced transparency requirements such as mandatory submission of a summary of the clinical trial results to the EU Database. The CTR foresees a three-year transition period. EU Member States will work in CTIS immediately after the system has gone live. Since January 31, 2023, submission of initial clinical trial applications via CTIS is mandatory, and by January 31, 2025, all ongoing trials approved under the former Clinical Trials Directive will need to comply with the CTR and have to be transitioned to CTIS. On July 19, 2023, the EC published guidance concerning the steps to be taken in this transition. This guidance provides, among other things, that (i) documentation which was previously assessed will not be reassessed, (ii) templates that were developed and endorsed by the EU Clinical Trials Expert Group to provide compliance with the CTR do not need to be updated and (iii) there is no need to retrospectively create a site suitability form, which are only necessary for new trial sites.

Under both the former regime and the new CTR, national laws, regulations, and the applicable GCP and GLP standards must also be respected during the conduct of the trials, including the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use ("ICH") guidelines on Good Clinical Practice and the ethical principles that have their origin in the Declaration of Helsinki.

During the development of a medicinal product, the EMA and national regulators within the EU provide the opportunity for dialogue and guidance on the development program. At the EMA level, this is usually done in the form of scientific advice, which is given by the Committee for Medicinal Products for Human Use (“CHMP”) on the recommendation of the Scientific Advice Working Party ("SAWP"). A fee is incurred with each scientific advice procedure, but is significantly reduced for designated orphan medicines. Advice from the EMA is typically provided based on questions concerning, for example, quality (chemistry, manufacturing and controls testing), nonclinical testing and clinical studies, and pharmacovigilance plans and risk-management programs. Advice is not legally binding with regard to any future Marketing Authorization Application (“MAA”) of the product concerned.

Drug Marketing Authorization

In the EEA, after completion of all required clinical testing, pharmaceutical products may only be placed on the market after obtaining a MA. To obtain a MA of a drug under European Union regulatory systems, an applicant can submit an MAA through, amongst others, a centralized or decentralized procedure.

To be used or sold in the UK, a drug must have an effective MA obtained by a centralized application through EMA or a national application. National applications are governed by the Human Medicines Regulations (SI 2012/1916). Applications are made electronically through the Medicines and Healthcare products Regulatory Agency (“MHRA”) Submissions Portal. The process from application to authorizations generally takes up to 210 days, excluding time taken to provide any additional information or data required by the MHRA.

On August 30, 2023, the MHRA published detailed guidance on its recently announced new International Reliance Procedure (“IRP”) for MAAs. The IRP applies since January 1, 2024 and replaces existing EU reliance procedures to apply for authorizations from seven international regulators (e.g. Health Canada, Swiss Medic, FDA, EMA, among others). The IRP allows medicinal products approved in other jurisdictions that meet certain criteria to undergo a fast-tracked MHRA review to obtain and/or update a MA in the UK or Great Britain.

Applicants can submit initial MAAs to the IRP but the procedure can also be used throughout the lifecycle of a product for post-authorization procedures including line extensions, variations and renewals.

Centralized Authorization Procedure

The centralized procedure provides for the grant of a single MA that is issued by the EC following the scientific assessment of the application by the EMA that is valid for all EU Member States as well as in the three additional EEA Member States. The centralized procedure is compulsory for certain types of medicinal products, including for medicines developed by means of certain biotechnological processes, products designated as orphan medicinal products, advanced therapy medicinal products ("ATMP") and medicinal products with a new active substance indicated for the treatment of certain diseases (AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and viral diseases). For medicinal products containing a new active substance not yet authorized in the EEA before May 20, 2004 and indicated for the treatment of other diseases, medicinal products that constitute significant therapeutic, scientific or technical innovations or for which the grant of a MA through the centralized procedure would be in the interest of public health at EU level, an applicant may voluntarily submit an application for a MA through the centralized procedure.

Under the centralized procedure, the CHMP established at the EMA, is responsible for conducting the initial assessment of a drug. The CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing MA. Under the centralized procedure, the timeframe for the evaluation of an MAA by the EMA’s CHMP is, in principle, 210 days from receipt of a valid MAA. However, this timeline excludes clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the CHMP, so the overall process typically takes a year or more, unless the application is eligible for an accelerated assessment. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest, particularly from the point of view of therapeutic innovation. Upon request, the CHMP can reduce the time frame to 150 days if the applicant provides sufficient justification for an accelerated assessment. The CHMP will provide a positive opinion regarding the application only if it meets certain quality, safety and efficacy requirements. This opinion is then transmitted to the EC, which has the ultimate authority for granting MA within 67 days after receipt of the CHMP opinion.

Decentralized Authorization Procedure

Medicines that fall outside the mandatory scope of the centralized procedure have three routes to authorization: (i) they can be authorized under the centralized procedure if they concern a significant therapeutic, scientific or technical innovation, or if their authorization would be in the interest of public health; (ii) they can be authorized under a decentralized procedure where an applicant applies for simultaneous authorization in more than one EU member state; or (iii) they can be authorized in an EU member state in accordance with that state’s national procedures and then be authorized in other EU countries by a procedure whereby the countries concerned agree to recognize the validity of the original, national MA (mutual recognition procedure).

The decentralized procedure permits companies to file identical MA applications for a medicinal product to the competent authorities in various EU Member States simultaneously if such medicinal product has not received marketing approval in any EU Member State before. This procedure is available for pharmaceutical

products not falling within the mandatory scope of the centralized procedure. The competent authority of a single EU Member State, the reference member state, is appointed to review the application and provide an assessment report. The competent authorities of the other EU Member States, the concerned member states, are subsequently required to grant a MA for their territories on the basis of this assessment. The only exception to this is where the competent authority of an EU Member State considers that there are concerns of potential serious risk to public health, the disputed points are subject to a dispute resolution mechanism and may eventually be referred to the EC, whose decision is binding for all EU Member States.

Risk Management Plan

All new MAAs must include a Risk Management Plan ("RMP") describing the risk management system that the company will put in place and documenting measures to prevent or minimize the risks associated with the product. RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available. An updated RMP must be submitted: (i) at the request of EMA or a national competent authority, or (ii) whenever the risk-management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit-risk profile or as a result of an important pharmacovigilance or risk-minimization milestone being reached. The regulatory authorities may also impose specific obligations as a condition of the MA. Since October 20, 2023, all RMPs for centrally authorized products are published by the EMA, subject only to limited redactions.

MA Validity Period

MAs have an initial duration of five years. After these five years, the authorization may subsequently be renewed on the basis of a reevaluation of the risk-benefit balance. Once renewed, the MA is valid for an unlimited period unless the EC or the national competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with only one additional five-year renewal. Applications for renewal must be made to the EMA at least nine months before the five-year period expires.

Additionally, the holder of a MA for an ATMP must put in place and maintain a system to ensure that each individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the relevant healthcare institution where the product is used.

Any authorization which is not followed by the actual placing of the drug on the EU market (in case of centralized procedure) or on the market of the authorizing member state within three years after authorization ceases to be valid.

For the UK, the period of three years during which the drug has not been marketed in Great Britain will be restarted from the date of conversion to a Great Britain MA. Conversion refers to the procedure by which, as of January 1, 2021, MAs granted on the basis of a centralized procedure in the EU are only valid in Norther Ireland but not in Great Britain, whereas, prior EU authorizations have all been automatically converted into UK MAs effective in Great Britain only.

On the other hand, for the EU, in the case the drug has been marketed in the UK, the placing on the UK market before the end of the period starting when the UK left the EU on January 31, 2020 and ending on December 31, 2020 (the "Brexit Transition Period") will be taken into account. If, after the end of the Brexit Transition Period, the drug is not placed on any other market of the remaining member states of the EU, the three year period will start running from the last date the drug was placed on the UK market before the end of the Brexit Transition Period.

Advanced Therapy Medicinal Products

In the EU, medicinal products, including ATMPs are subject to extensive pre- and post-market regulation by regulatory authorities at both the EU and national levels. ATMPs comprise gene therapy products, somatic cell therapy products and tissue engineered products, which are genes, cells or tissues that have undergone substantial manipulation and that are administered to human beings in order to cure, diagnose or prevent diseases or regenerate, repair or replace a human tissue. Pursuant to the ATMP Regulation, the Committee on Advanced Therapies ("CAT") is responsible in conjunction with the CHMP for the evaluation of ATMPs. The CHMP and CAT are also responsible for providing guidelines on ATMPs. These guidelines provide additional guidance on the factors that the EMA will consider in relation to the development and evaluation of ATMPs and include, among other things, the preclinical studies required to characterize ATMPs. Although such

guidelines are not legally binding, compliance with them is often necessary to gain and maintain approval for product candidates.

In addition to the mandatory RMP, the holder of a MA for an ATMP must put in place and maintain a system to ensure that each individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the relevant healthcare institution where the product is used.

Exceptional Circumstances/Conditional Approval

Similar to accelerated approval regulations in the United States, conditional MAs can be granted in the EU in exceptional circumstances. A conditional MA can be granted for medicinal products where, although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, a number of criteria are fulfilled: (i) the benefit/risk balance of the product is positive, (ii) it is likely that the applicant will be in a position to provide the comprehensive clinical data, (iii) unmet medical needs will be fulfilled by the grant of the MA 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 MA must be renewed annually.

Data and Market Exclusivity

As in the United States, it may be possible to obtain a period of market and / or data exclusivity in the EU that would have the effect of postponing the entry into the marketplace of a competitor’s generic, hybrid or biosimilar product (even if the pharmaceutical product has already received a MA) and prohibiting another applicant from relying on the MA holder’s pharmacological, toxicological and clinical data in support of another MA for the purposes of submitting an application, obtaining MA or placing the product on the market. New Chemical Entities ("NCEs") approved in the EU qualify for eight years of data exclusivity and 10 years of marketing exclusivity.

An additional non-cumulative one-year period of marketing exclusivity is possible if during the data exclusivity period (the first eight years of the 10-year marketing exclusivity period), the MA holder obtains an authorization for one or more new therapeutic indications that are deemed to bring a significant clinical benefit compared to existing therapies.

The data exclusivity period begins on the date of the product’s first MA in the EU. After eight years, a generic product application may be submitted and generic companies may rely on the MA holder’s data. However, a generic product cannot launch until two years later (or a total of 10 years after the first MA in the EU of the innovator product), or three years later (or a total of 11 years after the first MA in the EU of the innovator product) if the MA holder obtains MA for a new indication with significant clinical benefit within the eight-year data exclusivity period. Additionally, another non-cumulative one-year period of data exclusivity can be added to the eight years of data exclusivity where an application is made for a new indication for a well-established substance, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication. Another year of data exclusivity may be added to the eight years, where a change of classification of a pharmaceutical product has been authorized on the basis of significant pre-trial tests or clinical trials (when examining an application by another applicant for or holder of MA for a change of classification of the same substance the competent authority will not refer to the results of those tests or trials for one year after the initial change was authorized).

Products may not be granted data exclusivity since there is no guarantee that a product will be considered by the EU’s regulatory authorities to include a NCE. Even if a compound is considered to be a NCE and the MA applicant is able to gain the prescribed period of data exclusivity, another company nevertheless could also market another version of the medicinal product if such company can complete a full MAA with their own complete database of pharmaceutical tests, preclinical studies and clinical trials and obtain MA of its product.

On April 26, 2023, the EC submitted a proposal for the reform of the European pharmaceutical legislation. The current draft envisages e.g., a shortening of the periods of data exclusivity, however, there is currently neither a final version of this draft nor a date for its entry into force.

Orphan Designation and Exclusivity

The criteria for designating an orphan medicinal product in the EU are similar in principle to those in the U.S. The EMA grants orphan drug designation if the medicinal product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting no more than five in 10,000 persons in the EU (prevalence criterion). In addition, orphan drug designation can be granted if, for economic reasons, the medicinal product would be unlikely to be developed without incentives and if there is no other satisfactory method approved in the EU of diagnosing, preventing, or treating the condition, or if such a method exists, the proposed medicinal product is a significant benefit to patients affected by the condition. An application for orphan drug designation (which is not a MA, as not all orphan-designated medicines reach the authorization application stage) must be submitted first before an application for MA of the medicinal product is submitted. The applicant will receive a fee reduction for the MAA if the orphan drug designation has been granted, but not if the designation is still pending at the time the MA is submitted, and sponsors must submit an annual report to EMA summarizing the status of development of the medicine. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. Designated orphan medicines are eligible for conditional MA.

The EMA's Committee for Orphan Medicinal Products ("COMP") reassesses the orphan drug designation of a product in parallel with the review for a MA; for a product to benefit from market exclusivity it must maintain its orphan drug designation at the time of MA review by the EMA and approval by the EC. Additionally, any MA granted for an orphan medicinal product must only cover the therapeutic indication(s) that are covered by the orphan drug designation. Upon the grant of a MA, orphan drug designation provides up to ten years of market exclusivity in the orphan indication.

During the 10-year period of market exclusivity, with a limited number of exceptions, the regulatory authorities of the EU Member States and the EMA may not accept applications for MA, accept an application to extend an existing MA or grant a MA for other similar medicinal products for the same therapeutic indication. A similar medicinal product is defined as a medicinal product containing a similar active substance or substances as contained in a currently authorized orphan medicinal product, and which is intended for the same therapeutic indication. An orphan medicinal product can also obtain an additional two years of market exclusivity for an orphan-designated condition when the results of specific studies are reflected in the Summary of Product Characteristics ("SmPC") addressing the pediatric population and completed in accordance with a fully compliant Pediatric Investigation Plan ("PIP"). No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications.

The 10-year market exclusivity may 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, i.e. the condition prevalence or financial returns criteria under Article 3 of Regulation (EC) No. 141/2000 on orphan medicinal products. When the period of orphan market exclusivity for an indication ends, the orphan drug designation for that indication expires as well. Orphan exclusivity runs in parallel with normal rules on data exclusivity and market protection. Additionally, a MA may be granted to a similar medicinal product (orphan or not) for the same or overlapping indication subject to certain requirements.

In the UK, following the post-Brexit transition period, a system for incentivizing the development of orphan medicines was introduced. Overall, the requirements for orphan designation largely replicate the requirements in the EU and the benefit of market exclusivity has been retained. Products with an orphan designation in the EU can be considered for an orphan MA in Great Britain, but a UK-wide orphan MA can only be considered in the absence of an active EU orphan designation. The MHRA will review applications for orphan designation at the time of a MA, and will offer incentives, such as market exclusivity and full or partial refunds for MA fees to encourage the development of medicines in rare diseases.

Pediatric Development

In the EU, companies developing a new medicinal product are obligated to study their product in children and must therefore submit a PIP together with a request for agreement to the EMA. The EMA issues a decision on the PIP based on an opinion of the EMA's Pediatric Committee ("PDCO"). Companies must conduct pediatric clinical trials in accordance with the PIP approved by the EMA, unless a deferral (e.g. until enough information to demonstrate its effectiveness and safety in adults is available) or waiver (e.g. because the relevant disease or condition occurs only in adults) has been granted by the EMA. The MAA for the medicinal product must include the results of all pediatric clinical trials performed and details of all information collected in compliance with the approved PIP, unless a waiver or a deferral has been granted, in which case the pediatric clinical trials may be completed at a later date. Medicinal products that are granted an MA on the basis of the pediatric clinical trials conducted in accordance with the approved PIP are eligible for a six month extension of

the protection under a supplementary protection certificate (if any is in effect at the time of approval), or, in the case of orphan medicinal products, a two year extension of the orphan market exclusivity. This pediatric reward is subject to specific conditions and is not automatically available when data in compliance with the approved PIP are developed and submitted. An approved PIP is also required when a MA holder wants to add a new indication, medicinal form or route of administration for a medicine that is already authorized and covered by intellectual property rights.

In the UK, the MHRA has published guidance on the procedures for UK PIPs which, where possible, mirror the submission format and requirements of the EU system. EU PIPs remain applicable for Northern Ireland and EU PIPs agreed by the EMA prior to January 1, 2021 have been adopted as UK PIPs.

PRIME Designation

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 (“PRIME”) scheme is intended to encourage drug development in areas of unmet medical need and provides accelerated assessment of products representing substantial innovation reviewed under the centralized procedure. Products from small- and medium-sized enterprises may qualify for earlier entry into the PRIME scheme than larger companies on the basis of compelling non-clinical data and tolerability data from initial clinical trials. 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 potentially accelerated MAA assessment once a dossier has been submitted. Importantly, once a candidate medicine has been selected for the PRIME scheme, a dedicated contact point and rapporteur from the CHMP or CAT are appointed facilitating increased understanding of the product at EMA’s Committee level. A kick-off meeting with the CHMP/CAT rapporteur initiates these relationships and includes a team of multidisciplinary experts to provide guidance on the overall development plan and regulatory strategy. PRIME eligibility does not change the standards for product approval, and there is no assurance that any such designation or eligibility will result in expedited review or approval.

Post-Approval Regulation

Similar to the United States, both MA holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA, the EC and/or the competent regulatory authorities of the EU Member States. This oversight applies both before and after grant of manufacturing licenses and MAs. It includes control of compliance with EU good manufacturing practices rules, manufacturing authorizations, pharmacovigilance rules and requirements governing advertising, promotion, sale, and distribution, recordkeeping, importing and exporting of medicinal products.

Failure by us or by any of our third-party partners, including suppliers, manufacturers and distributors to comply with EU laws and the related national laws of individual EU Member States governing the conduct of clinical trials, manufacturing approval, MA of medicinal products and marketing of such products, both before and after grant of MA, statutory health insurance, bribery and anti-corruption or other applicable regulatory requirements may result in administrative, civil or criminal penalties. These penalties could include delays or refusal to authorize the conduct of clinical trials or to grant MA, product withdrawals and recalls, product seizures, suspension, withdrawal or variation of the MA, total or partial suspension of production, distribution, manufacturing or clinical trials, operating restrictions, injunctions, suspension of licenses, fines and criminal penalties.

The holder of MA for a medicinal product must also comply with EU pharmacovigilance legislation and its related regulations and guidelines, which entail many requirements for conducting pharmacovigilance, or the assessment and monitoring of the safety of medicinal products.

These pharmacovigilance rules can impose on holders of MAs the obligation to conduct a labor intensive collection of data regarding the risks and benefits of marketed medicinal products and to engage in ongoing assessments of those risks and benefits, including the possible requirement to conduct additional clinical studies or post-authorization safety studies to obtain further information on a medicine’s safety, or to measure the effectiveness of risk-management measures, which may be time consuming and expensive and could impact our profitability. MA holders must establish and maintain a pharmacovigilance system and appoint an individual qualified person for pharmacovigilance, who is responsible for oversight of that system. Key obligations include expedited reporting of suspected serious adverse reactions and submission of Periodic Safety Update Reports ("PSURs") in relation to medicinal products for which they hold MAs. The EMA reviews

PSURs for medicinal products authorized through the centralized procedure. If the EMA has concerns that the risk benefit profile of a product has varied, it can adopt an opinion advising that the existing MA for the product be suspended, withdrawn or varied. The agency can advise that the MA holder be obliged to conduct post-authorization Phase IV safety studies. If the EC agrees with the opinion, it can adopt a decision varying the existing MA. Failure by the MA holder to fulfill the obligations for which the EC's decision provides can undermine the ongoing validity of the MA.

More generally, non-compliance with pharmacovigilance obligations can lead to the variation, suspension or withdrawal of the MA for the product or imposition of financial penalties or other enforcement measures.

The manufacturing process for pharmaceutical products in the EU is highly regulated and regulators may shut down manufacturing facilities that they believe do not comply with regulations. Manufacturing requires a manufacturing authorization, and the manufacturing authorization holder must comply with various requirements set out in the applicable EU laws, regulations and guidance, including Directive 2001/83/EC, Directive 2003/94/EC, Regulation (EC) No 726/2004 and the European Commission Guidelines for Good Manufacturing Practice ("GMP"). These requirements include compliance with EU GMP standards when manufacturing pharmaceutical 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. Similarly, the distribution of pharmaceutical products into and within the EU is subject to compliance with the applicable EU laws, regulations and guidelines, including the requirement to hold appropriate authorizations for distribution granted by the competent authorities of the EU Member States. The manufacturer or importer must have a qualified person who is responsible for certifying that each batch of product has been manufactured in accordance with GMP, before releasing the product for commercial distribution in the EU or for use in a clinical trial. Manufacturing facilities are subject to periodic inspections by the competent authorities for compliance with GMP.

Sales and Marketing Regulations

The advertising and promotion of our products is also subject to EU laws concerning promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices. In addition, other national legislation of individual EU Member States may apply to the advertising and promotion of medicinal products and may differ from one country to another. These laws require that promotional materials and advertising in relation to medicinal products comply with the product's SmPC as approved by the competent regulatory authorities. The SmPC is the document that provides information to physicians concerning the safe and effective use of the medicinal product. It forms an intrinsic and integral part of the MA granted for the medicinal product. Promotion of a medicinal product that does not comply with the SmPC is considered to constitute off-label promotion. All advertising and promotional activities for the product must be consistent with the approved SmPC and therefore all off-label promotion is prohibited. Direct-to-consumer advertising of prescription-only medicines is also prohibited in the EU. Violations of the rules governing the promotion of medicinal products in the EU could be penalized by administrative measures, fines and imprisonment. These laws may further limit or restrict the advertising and promotion of our products to the general public and may also impose limitations on its promotional activities with healthcare professionals.

EU regulation with regards to dispensing, sale and purchase of medicines has generally been preserved in the UK following Brexit, through the Human Medicines Regulations 2012. However, organizations wishing to sell medicines online need to register with the MHRA. Following Brexit, the requirements to display the common logo no longer apply to UK-based online sellers, except for those established in Northern Ireland.

Anti-Corruption Legislation

In the EU, interactions between pharmaceutical companies and physicians are also governed by strict laws, regulations, industry self-regulation codes of conduct and physicians' codes of professional conduct both at EU level and in the individual EU Member States. The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is prohibited in the EU. The provision of benefits or advantages to physicians is also governed by the national anti-bribery laws of the EU Member States. Violation of these laws could result in substantial fines and imprisonment.

Payments made to physicians in certain EU Member States also must be publicly disclosed. Moreover, agreements with physicians must often be the subject of prior notification and approval by the physician's employer, his/her regulatory professional organization, and/or the competent authorities of the individual EU

Member States. These requirements are provided in the national laws, industry codes, or professional codes of conduct, applicable in the individual EU Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

In the UK, the pharmaceutical sector is recognized as being particularly vulnerable to corrupt practices, some of which fall within the scope of the Bribery Act 2010. Due to the Bribery Act 2010's far-reaching territorial application, the potential penalized act does not have to occur in the UK to become within its scope. If the act or omission does not take place in the UK, but the person's act or omission would constitute an offense if carried out there and the person has a close connection with the UK, an offense will still have been committed.

The Bribery Act 2010 is comprised of four offenses that cover (i) individuals, companies and partnerships that give, promise or offer bribes, (ii) individuals, companies and partnerships that request, agree to receive or accept bribes, (iii) individuals, companies and partnerships that bribe foreign public officials, and (iv) companies and partnerships that fail to prevent persons acting on their behalf from paying bribes. The penalties imposed under the Bribery Act 2010 depend on the offence committed, harm and culpability and penalties range from unlimited fines to imprisonment for a maximum term of ten years and in some cases both.

Regulations in the UK and Other Markets

The UK formally left the EU on January 31, 2020 and EU laws now only apply to the UK in respect of Northern Ireland as laid out in the Protocol on Ireland and Northern Ireland and as amended by the Windsor Framework sets out a long-term set of arrangements for the supply of medicines into Northern Ireland. The EU and the UK agreed on a trade and cooperation agreement ("TCA"), which includes provisions affecting the life sciences sector (including on customs and tariffs). There are some specific provisions concerning pharmaceuticals, including the mutual recognition of GMP, inspections of manufacturing facilities for medicinal products and GMP issued documents. The TCA does not, however, contain wholesale mutual recognition of UK and EU pharmaceutical regulations and product standards.

The UK government has adopted the Medicines and Medical Devices Act 2021 (the "MMDA") to enable the UK's regulatory frameworks to be updated following the UK's departure from the EU. The MMDA introduces regulation-making, delegated powers covering the fields of human medicines, clinical trials of human medicines, veterinary medicines and medical devices. The MHRA has since been consulting on future regulations for medicines and medical devices in the UK.

For other countries outside of the EU, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, again, the clinical trials must be conducted in accordance with GCPs and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension of clinical trials, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Available Information

We file Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other information with the U.S. Securities and Exchange Commission ("SEC"). Our filings with the SEC are available free of charge on the SEC's website at *www.sec.gov* and on our website under the "Investors & Media" tab as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC.

Item 1A. Risk Factors

The following summarizes the principal factors that make an investment in the Company speculative or risky, all of which are more fully described in the Risk Factors section below. This summary should be read in conjunction with the Risk Factors section and should not be relied upon as an exhaustive summary of the material risks facing our business. The occurrence of any of these risks, could harm our business, financial condition, results of operations and/or growth prospects or cause our actual results to differ materially from those contained in forward-looking statements we have made in this Annual Report on Form 10-K and those we may make from time to time. You should consider all of the risk factors described in our public filings when evaluating our business.

Risk Factor Summary

Risks Related to Our Financial Condition and Capital Requirements

- We will not be able to continue as a going concern if we are unable to raise additional capital when needed.
- We have never generated any revenue from product sales and may never be profitable.
- We anticipate that we will continue to incur significant losses for the foreseeable future.
- We may not be able to raise the capital that we need to support our business plans and raising additional capital may cause dilution to our stockholders and restrict our operations.

Risks Related to the Discovery, Development and Commercialization

- We face competition from companies that have developed or may develop competing programs.
- Our programs are in preclinical stages of development and may fail in development or suffer delays.
- We are substantially dependent on the success of the SPY001 and SPY002 programs.
- We may fail to achieve our projected development goals in the time frames we announce and expect.
- Any drug delivery device potentially used may have its own regulatory development, supply, and other risks.
- We may not be successful in our efforts to build a pipeline of product candidates with commercial value.
- Our studies and trials may not be sufficient to support regulatory approval of any of our product candidates.
- If we are unable to successfully develop complementary diagnostics for our therapeutic product candidates, we may not realize their full commercial potential.
- We have limited experience in developing and commercializing diagnostics and have never applied for or obtained regulatory clearance or approval for any diagnostic tests.
- Additional time may be required to obtain regulatory approval for our product candidates and future product candidates because of their status as combination products.
- We may encounter difficulties enrolling participants in our future clinical trials.
- Preliminary or “topline” data from our clinical trials may change as more data becomes available.
- Our future clinical trials may reveal significant adverse events or side effects.
- We may fail to capitalize on more profitable or potentially successful product candidates than those we pursue.
- Any of our future approved products may not achieve regulatory approval, market acceptance or commercial success.
- Certain of our programs may compete with our other programs.
- The FDA may not accept data from clinical trials we conduct at sites outside the United States.

Risks Related to Government Regulation

- FDA and comparable foreign regulatory approval processes are lengthy and time-consuming and we may not be able to obtain, or may be delayed in obtaining, regulatory approvals for our product candidates.
- We may not be able to meet requirements for chemistry, manufacturing and control of our programs.
- Our product candidates may face competition sooner than anticipated based on rules and regulations that may apply or government decisions with respect to our intellectual property.
- Even if we receive regulatory approval, we will be subject to extensive ongoing regulatory obligations.
- We may face difficulties from healthcare legislative reform measures.
- Our operations and arrangements with third-parties are subject to healthcare regulatory laws.
- We may be unable to offer products at competitive prices due to unfavorable pricing regulations and/or third-party coverage and reimbursement policies.

- We may face criminal liability or other consequences for violations of U.S. and foreign trade regulations.
- Foreign governments may impose strict price controls, which may adversely affect our revenue.
- Any accelerated review designations (e.g. fast track designation) we may pursue may not hasten development or regulatory review.

Risks Related to Our Intellectual Property

- Our ability to obtain and protect our patents and other proprietary rights is uncertain.
- We may fail in obtaining or maintaining necessary rights to our programs.
- We may be subject to patent infringement claims or may need to file such claims.
- We may be subject to claims of wrongful hiring of employees or wrongful use of confidential information.
- Our patents and our ability to protect our products may be impaired by changes to patent laws.
- Our patent protection could be reduced or eliminated for non-compliance with regulatory requirements.
- We may fail to identify or interpret relevant third-party patents.
- We may become subject to claims challenging the inventorship or ownership of our intellectual property.
- Patent terms may be inadequate to protect our competitive position of our programs.
- Our technology licensed from various third parties may be subject to retained rights.

Risks Related to Our Reliance on Third Parties

- We may fail to maintain collaborations and licensing arrangements with third parties that we rely on.
- Third-parties we rely on for the execution of preclinical studies and clinical trials may fail to carry out their contractual duties.
- We may be unable to use third-party manufacturing sites or our third-party manufacturers may encounter difficulties in production.

Risks Related to Employee Matters, Managing Growth and Other Risks Related to Our Business

- We may experience difficulties in managing the growth of our organization.
- We may fail to attract or retain highly qualified personnel.
- Our ability to operate in foreign markets is subject to regulatory burdens, risks and uncertainties.
- Our estimates of market opportunity and forecasts of market growth may be inaccurate and our business may not grow at similar rates, or at all.
- Our employees or third-parties may engage in misconduct or other improper activities.
- We may be impacted by security or data breaches or other improper access to our data.
- Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.
- We may fail to comply with privacy and data security regulations.
- We may fail to comply with environmental, health and safety laws and regulations.
- We may be subject to adverse legislative or regulatory tax changes.
- We may fail to realize the benefits of our business or product acquisitions or our strategic alliances.
- We may be impacted by the failure of financial institutions.

Risks Related to Our Common Stock

- We may fail to obtain stockholder approval of the conversion of our Series B Preferred Stock.
- Our certificate of incorporation, Delaware law and certain contracts include anti-takeover provisions.
- Our certificate of incorporation and bylaws contain exclusive forum provisions.
- We do not anticipate paying any dividends in the foreseeable future.
- Future sales of shares by existing stockholders could cause our stock price to decline.
- Future sales and issuances of equity and debt could result in additional dilution to our stockholders.
- Our principal stockholders own a significant percentage of our stock.

General Risk Factors

- The market price of our common stock has historically been volatile and may drop in the future.
- We incur significant costs associated with complying with public company reporting requirements.
- A lack of analyst coverage may cause a decline in our stock price or trading volume.
- We may fail to maintain proper and effective internal controls.

Risks Related to Our Financial Condition and Capital Requirements

We will need to raise additional capital, and if we are unable to do so when needed, we will not be able to continue as a going concern.

This Annual Report includes disclosures regarding our management's assessment of our ability to continue as a going concern. As of December 31, 2023, we had $339.6 million of cash, cash equivalents, marketable securities, and restricted cash. We will need to raise additional capital to continue to fund our operations and service our debt obligations in the future. If we are unable to raise additional capital when needed, we will not be able to continue as a going concern.

Developing our product candidates requires a substantial amount of capital. We expect our research and development expenses to increase in connection with our ongoing activities, particularly as we advance our product candidates through clinical trials. We will need to raise additional capital to fund our operations and such funding may not be available to us on acceptable terms, or at all, and such funding may become even more difficult to obtain due to rising interest rates and the current downturn in the U.S. capital markets and the biotechnology sector in general. Competition for additional capital among biotechnology companies may be particularly intense during this present economic downturn. We may be unable to raise capital through public offerings of our common stock and may need to turn to alternative financing arrangements. Such arrangements, if we pursue them, 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. Interest on any newly-issued debt securities and/or newly-incurred borrowings would increase our operating costs and reduce our net income (or increase our net loss), 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.

We do not currently have any products approved for sale and do not generate any revenue from product sales. Accordingly, we expect to rely primarily on equity and/or debt financings to fund our continued operations. Our ability to raise additional funds will depend, in part, on the success of our preclinical studies and clinical trials and other product development activities, regulatory events, our ability to identify and enter into licensing or other strategic arrangements, and other events or conditions that may affect our value or prospects, as well as factors related to financial, economic and market conditions, many of which are beyond our control. There can be no assurances that sufficient funds will be available to us when required or on acceptable terms, if at all.

If we are unable to raise additional capital when required or on acceptable terms, we may be required to:

- significantly delay, scale back, or discontinue the development or commercialization of our product candidates;
- seek strategic partnerships, or amend existing partnerships, for research and development programs at an earlier stage than otherwise would be desirable or that we otherwise would have sought to develop independently, or on terms that are less favorable than might otherwise be available in the future;
- dispose of technology assets, or relinquish or license on unfavorable terms, our rights to technologies or any of our product candidates that we otherwise would seek to develop or commercialize ourselves;
- pursue the sale of our company to a third party at a price that may result in a loss on investment for our stockholders; or
- file for bankruptcy or cease operations altogether (and face any related legal proceedings).

Any of these events could have a material adverse effect on our business, operating results and prospects.

Even if successful in raising new capital, we could be limited in the amount of capital we raise due to investor demand restrictions placed on the amount of capital we raise or other reasons.

Additionally, any capital raising efforts are subject to significant risks and contingencies, as described in more detail under the risk factor titled “Raising additional capital may cause dilution to our stockholders, restrict our operations, or require us to relinquish rights.”

We have never generated any revenue from product sales and may never be profitable.

We have no products approved for commercialization and have never generated any revenue from product sales. Our ability to generate revenue and achieve profitability depends on our ability, alone or with strategic collaborators, to successfully complete the development of, and obtain the regulatory and marketing approvals necessary to commercialize one or more of our product candidates. We do not anticipate generating revenue from product sales for the foreseeable future. Our ability to generate future revenue from product sales depends heavily on our success in many areas, including but not limited to:

- completing research and development of our product candidates;
- obtaining regulatory and marketing approvals for our product candidates for which we complete clinical trials;
- manufacturing product candidates and establishing and maintaining supply and manufacturing relationships with third parties that are commercially feasible, meet regulatory requirements and our supply needs in sufficient quantities to meet market demand for our product candidates, if approved;
- qualify for adequate coverage and reimbursement by government and third-party payors for any product candidates for which we obtain regulatory and marketing approval;
- marketing, launching, and commercializing product candidates for which we obtain regulatory and marketing approval, either directly or with a collaborator or distributor;
- gaining market acceptance of our product candidates as treatment options;
- addressing any competing products and technological and market developments;
- implementing internal systems and infrastructure, as needed;
- protecting and enforcing our intellectual property rights, including patents, trade secrets, and know-how;
- negotiating favorable terms in any collaboration, licensing, or other arrangements into which we may enter;
- obtaining coverage and adequate reimbursement from third-party payors and maintaining pricing for our product candidates that supports profitability; and
- attracting, hiring, and retaining qualified personnel.

Even if one or more of the product candidates that we develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate. Our expenses could increase beyond expectations if we are required by regulatory authorities to perform clinical and other studies in addition to those that we anticipate. Even if we are able to generate revenues from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations. Portions of the research programs with respect to which we have exercised the Option to acquire intellectual property license rights to or have the Option to acquire intellectual property license rights to pursuant to the Paragon Agreement may be in-licensed from third parties, which make the commercial sale of such in-licensed products potentially subject to additional royalty and milestone payments to such third parties. We will also have to develop or acquire manufacturing capabilities or continue to contract with contract manufacturers in order to continue development and potential commercialization of our product candidates. For instance, if the costs of manufacturing our drug product are not commercially feasible, we will need to develop or procure our drug product in a commercially feasible manner in order to successfully commercialize a future approved product, if any. Additionally, if we are not able to generate revenue from the sale of any approved products, we may never become profitable.

We have historically incurred losses, have a limited operating history on which to assess our business, and anticipate that we will continue to incur significant losses for the foreseeable future.

We are a biopharmaceutical company with a limited operating history. Since inception, we have incurred significant operating losses. For the years ended December 31, 2023, 2022 and 2021, we reported a net loss of $338.8 million, $83.8 million and $65.8 million, respectively. As of December 31, 2023, we had an accumulated deficit of $764.4 million. We will need to raise substantial additional capital to continue to fund our operations in the future. If our stockholders do not timely approve the conversion of our Series B Preferred Stock, then the holders of our Series B Preferred Stock may be entitled to require us to settle their shares of Series B Preferred Stock for cash at a price per underlying share of common stock equal to the last reported closing sale price of common stock on the principal trading market on which the common stock is listed as of the trading day immediately prior to the date on which a request to convert shares of Series B Preferred Stock into shares of common stock is delivered to us by a holder in accordance with the terms of the Series B Certificate of Designation and we fail to deliver such shares of common stock, as described in our Series B Certificate of Designation relating to the Series B Preferred Stock. Because the specific timing of the exercise of the cash redemption is not under our control and is dependent the closing sale price of our common stock at the time of such conversion, we cannot quantify the aggregate amount of the potential cash settlement; however, for illustrative purposes only, if all of our holders of Series B Preferred Stock had delivered requests to convert their shares of Series B Preferred Stock on February 26, 2024 and assuming we were obligated to settle such conversions in cash pursuant to the terms of the Series B Certificate of Designation, a total of $141,480,000 would have been payable to such holders as a result of the cash settlement of all 6,000,000 shares of common stock issuable upon the conversion of 150,000 shares of Series B Preferred Stock, at a price of $23.58 per share of common stock, which was the closing sale price of our common stock on the Nasdaq Global Select Market on February 23, 2024.

Failure to raise capital as and when needed, on favorable terms or at all, would have a negative impact on our financial condition and our ability to develop our product candidates. Changing circumstances may cause us to consume capital significantly faster or slower than we currently anticipate. If we are unable to acquire additional capital or resources, we will be required to modify our operational plans to complete future milestones and we may be required to delay, limit, reduce or eliminate development or future commercialization efforts of product candidates and/or programs. We have based these estimates on assumptions that may prove to be wrong, and we could exhaust our available financial resources sooner than we currently anticipate. We may be forced to reduce our operating expenses and raise additional funds to meet our working capital needs, principally through the additional sales of our securities or debt financings or entering into strategic collaborations.

We have devoted substantially all of our financial resources to identify, acquire, and develop our product candidates, including conducting preclinical and clinical development of the legacy rare disease clinical studies conducted by us prior to the Asset Acquisition (the "Legacy Pipeline") and the preclinical development of our current IBD pipeline, and providing general and administrative support for our operations. To date, we have funded our operations primarily from the sale and issuance of convertible preferred and common equity securities, pre-funded warrants, the collection of grant proceeds, and the licensing of our product rights for commercialization of pegzilarginase in Europe and certain countries in the Middle East. The amount of our future net losses will depend, in part, on the rate of our future expenditures and our ability to obtain funding through equity or debt financings, strategic collaborations, or grants. Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. We expect our losses to increase as our product candidates enter more advanced clinical trials. It may be several years, if ever, before we complete pivotal clinical trials or have a product candidate approved for commercialization. We expect to invest significant funds into the research and development of our current product candidates to determine the potential to advance these product candidates to regulatory approval.

If we obtain regulatory approval to market a product candidate, our future revenue will depend upon the size of any markets in which our product candidates may receive approval, and our ability to achieve sufficient market acceptance, pricing, coverage and adequate reimbursement from third-party payors, and adequate market share for our product candidates in those markets. Even if we obtain adequate market share for our product candidates, because the potential markets in which our product candidates may ultimately receive regulatory approval could be very small, we may never become profitable despite obtaining such market share and acceptance of our products.

We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future and our expenses will increase substantially if and as we:

- continue the preclinical development and initiate the clinical development of our product candidates;
- continue efforts to discover and develop new product candidates;
- continue the manufacturing of our product candidates or increase volumes manufactured by third parties;
- advance our product candidates into larger, more expensive clinical trials;
- initiate additional preclinical studies or clinical trials for our product candidates;
- seek regulatory and marketing approvals and reimbursement for our product candidates;
- establish a sales, marketing, and distribution infrastructure to commercialize any products for which we may obtain marketing approval and market for ourselves;
- seek to identify, assess, acquire, and/or develop other product candidates;
- make milestone, royalty, or other payments under third-party license agreements;
- seek to maintain, protect, and expand our intellectual property portfolio;
- pay penalties under our registration rights agreement for failing to timely register the applicable securities;
- seek to attract and retain skilled personnel; and
- experience any delays or encounter issues with the development and potential for regulatory approval of our clinical and product candidates such as safety issues, manufacturing delays, clinical trial accrual delays, longer follow-up for planned studies or trials, additional major studies or trials, or supportive trials necessary to support marketing approval.

Further, the net losses we incur may fluctuate significantly from quarter to quarter and year to year, such that a period-to-period comparison of our results of operations may not be a good indication of our future performance.

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

Until such time, if ever, as we can generate substantial revenue from the sale of our product candidates, we expect to finance our cash needs through a combination of equity offerings, debt financings and license and development agreements. To the extent that we raise additional capital through the sale of equity securities or convertible debt securities, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a holder of common stock. 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, 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 be required to relinquish valuable rights to our 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 or other arrangements with third parties when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to third parties to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

To the extent that we raise additional capital through the sale of equity, including pursuant to any sales under convertible debt or other securities convertible into equity, the ownership interest of our stockholders will be diluted, and the terms of these new securities may include liquidation or other preferences that adversely affect the rights of our stockholders. For instance, in December 2023, we sold an aggregate of 6,000,000 shares of common stock and 150,000 shares of our Series B Preferred Stock in the December 2023 PIPE to the

December 2023 Investors for gross proceeds of $180.0 million. Subject to receiving the requisite stockholder approval and certain beneficial ownership limitations set by each holder of Series B Preferred Stock, each share of Series B Preferred Stock will automatically convert into an aggregate of 40 shares of our common stock. We are required to solicit the consent of our stockholders with regard to conversion of the shares of our Series B Preferred Stock which will be voted on at our 2024 annual meeting of stockholders. If our stockholders fail to approve such matters, we may be subject to financial penalties that could materially harm our business, including the forced settlement of shares of Series B Preferred Stock for cash, as described in our Series B Certificate of Designation.

Debt financing, if available, would likely involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures, making additional product acquisitions, or declaring dividends. If we raise additional funds through strategic collaborations or licensing arrangements with third parties, we may have to relinquish valuable rights to our product candidates or future revenue streams or grant licenses on terms that are not favorable to us. We cannot be assured that we will be able to obtain additional funding if and when necessary to fund our entire portfolio of product candidates to meet our projected plans. If we are unable to obtain funding on a timely basis, we may be required to delay or discontinue one or more of our development programs or the commercialization of any product candidates or be unable to expand our operations or otherwise capitalize on potential business opportunities, which could materially harm our business, financial condition, and results of operations.

Risks Related to Discovery, Development and Commercialization

We face competition from entities that have developed or may develop programs for the diseases addressed by our product candidates.

The development and commercialization of drugs is highly competitive. Our product candidates, if approved, will face significant competition and our failure to effectively compete may prevent us from achieving significant market penetration. We compete with a variety of multinational biopharmaceutical companies, specialized biotechnology companies and emerging biotechnology companies, as well as academic institutions, governmental agencies, and public and private research institutions, among others. Many of the companies with which we are currently competing or will complete against in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, clinical trial conduct, regulatory approvals, and marketing 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, establishing clinical trial sites, recruiting participants for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our product candidates.

Our competitors have developed, are developing or will develop programs and processes competitive with our programs and processes. Competitive therapeutic treatments include those that have already been approved and accepted by the medical community and any new treatments. Our success will depend partially on our ability to develop and commercialize products that have a competitive safety, efficacy, dosing and/or presentation profile. Our commercial opportunity and success will be reduced or eliminated if competing products are safer, more effective, have a more attractive dosing profile or presentation or are less expensive than the products we develop, or if our competitors develop competing products or if biosimilars enter the market more quickly than we do and are able to gain market acceptance. See the section titled “Business – Competition” for more discussion about our competitors.

In addition, because of the competitive landscape for inflammatory and immunology ("I&I") indications, we may also face competition for clinical trial enrollment. Clinical trial enrollment will depend on many factors, including if potential clinical trial participants choose to undergo treatment with approved products or enroll in competitors’ ongoing clinical trials for programs that are under development for the same indications as our programs. An increase in the number of approved products for the indications we are targeting with our programs may further exacerbate this competition. Our inability to enroll a sufficient number of participants could, among other things, delay our development timeline, which may further harm our competitive position.

Our product candidates are in preclinical stages of development and may fail in development or suffer delays that materially and adversely affect their commercial viability. If we or our current or future

collaborators are unable to complete development of, or commercialize our product candidates, or experience significant delays in doing so, our business will be materially harmed.

We have no products on the market, and all of our product candidates are in preclinical stages of development and have not been tested in humans. As a result, we expect it will be many years before we commercialize any product candidate, if ever. Our ability to achieve and sustain profitability depends on obtaining regulatory approvals for, and successfully commercializing, our product candidates, either alone or with third parties, and we cannot guarantee you that we will ever obtain regulatory approval for any of our product candidates. We have not yet demonstrated our ability to initiate or complete any clinical trials, obtain regulatory approvals, manufacture a clinical or 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. Before obtaining regulatory approval for the commercial distribution of our product candidates, we or an existing or future collaborator must conduct extensive preclinical tests and clinical trials to demonstrate the safety and efficacy in humans of our programs and future product candidates.

We or our collaborators may experience delays in initiating or completing clinical trials. We or our collaborators also may experience numerous unforeseen events during, or as a result of, any current or future clinical trials that we could conduct that could delay or prevent our ability to receive marketing approval or commercialize our current product candidates or any future product candidates, including:

- regulators or institutional review boards ("IRBs"), the FDA or ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching, or fail to reach, agreement on acceptable terms with prospective trial sites and prospective contract research organizations ("CROs"), the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- clinical trial sites deviating from trial protocol or dropping out of a trial;
- clinical trials of any product candidates may fail to show safety or efficacy, produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional preclinical studies or clinical trials or we may decide to abandon product development programs;
- the number of subjects required for clinical trials of any product candidates may be larger than we anticipate, especially if regulatory bodies require completion of non-inferiority or superiority trials, enrollment in these clinical trials may be slower than we anticipate or subjects may drop out of these clinical trials or fail to return for post-treatment follow-up 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, or may deviate from the clinical trial protocol or drop out of the trial, which may require that we add new clinical trial sites or investigators;
- we may elect to, or regulators, IRBs or ethics committees may require that we or our investigators, suspend or terminate clinical research or trials for various reasons, including noncompliance with regulatory requirements or a finding that the participants in our trials are being exposed to unacceptable health risks;
- the cost of clinical trials of any of our programs may be greater than we anticipate;
- the quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be inadequate to initiate or complete a given clinical trial;
- our inability to manufacture sufficient quantities of our product candidates for use in clinical trials;

- reports from clinical testing of other therapies may raise safety or efficacy concerns about our programs;
- our failure to establish an appropriate safety profile for a product candidate based on clinical or preclinical data for such product candidates as well as data emerging from other therapies in the same class as our product candidates; and
- the FDA or other regulatory authorities may require us to submit additional data such as long-term toxicology studies, or impose other requirements before permitting us to initiate a clinical trial.

Commencing clinical trials in the United States is subject to acceptance by the FDA of an IND, BLA or similar application and finalizing the trial design based on discussions with the FDA and other regulatory authorities. In the event that the FDA requires us to complete additional preclinical studies or we are required to satisfy other FDA requests prior to commencing clinical trials, the start of our first clinical trials may be delayed. Even after we receive and incorporate guidance from these regulatory authorities, the FDA or other regulatory authorities could disagree that we have satisfied their requirements to commence any clinical trial or change their position on the acceptability of our trial design or the clinical endpoints selected, which may require us to complete additional preclinical studies or clinical trials, delay the enrollment of our clinical trials or impose stricter approval conditions than we currently expect. There are equivalent processes and risks applicable to clinical trial applications in other countries, including countries in the EU.

We may not have the financial resources to continue development of, or to modify existing or enter into new collaborations for, a product candidate if we experience any issues that delay or prevent regulatory approval of, or our ability to commercialize, our product candidates. We or our current or future collaborators' inability to complete development of, or commercialize our product candidates, or significant delays in doing so, could have a material and adverse effect on our business, financial condition, results of operations and prospects.

We are substantially dependent on the success of our two most advanced programs, SPY001 and SPY002, and our anticipated clinical trials of such programs may not be successful.

Our future success is substantially dependent on our ability to timely obtain marketing approval for, and then successfully commercialize, our two most advanced programs, SPY001 and SPY002. We exercised our Option with respect to the SPY001 and SPY002 programs on July 12, 2023 and December 14, 2023, respectively. We are investing a majority of our efforts and financial resources into the research and development of these programs. We anticipate initiating a Phase 1 clinical trial in healthy volunteers of SPY001 in the first half of 2024 and of SPY002 in the second half of 2024, each subject to the filing of an IND or foreign equivalent and regulatory approval. The success of our programs is dependent on observing a longer half-life of our product candidates in humans than other mAbs currently marketed and in development as we believe this longer half-life has the potential to result in a more favorable dosing schedule for our product candidates, assuming they successfully complete clinical development and obtain marketing approval. This is based in part on the assumption that the longer half-life we have observed in non-human primates ("NHPs") will translate into an extended half-life of our product candidates in humans. To the extent we do not observe this extended half-life when we dose humans with our product candidates, it would significantly and adversely affect the clinical and commercial potential of our product candidates.

Our programs will require additional clinical development, evaluation of clinical, preclinical and manufacturing activities, product development, marketing approval in multiple jurisdictions, substantial investment and significant marketing efforts before we generate any revenues from product sales. We are not permitted to market or promote these programs, or any other programs, before we receive marketing approval from the FDA and comparable foreign regulatory authorities, and we may never receive such marketing approvals.

The success of our product candidates will depend on a variety of factors. We do not have complete control over many of these factors, including certain aspects of clinical development and the regulatory submission process, potential threats to our intellectual property rights and the manufacturing, marketing, distribution and sales efforts of any current or future collaborator. Accordingly, we cannot assure you that we will ever be able to generate revenue through the sale of these product candidates, even if approved. If we are not successful in commercializing our SPY001 or SPY002 programs, or are significantly delayed in doing so, our business will be materially harmed.

If we do not achieve our projected development goals in the time frames we announce and expect, the commercialization of our product candidates may be delayed and our expenses may increase and, as a result, our stock price may decline.

From time to time, we estimate the timing of the anticipated accomplishment of various scientific, clinical, regulatory and other product development goals, which we sometimes refer to as milestones. These milestones may include the commencement or completion of scientific studies and clinical trials, such as the expected timing for the anticipated commencement of our Phase 1 study, clinical trials in IBD, as well as the submission of regulatory filings. From time to time, we may publicly announce the expected timing of some of these milestones. All of these milestones are and will be based on numerous assumptions. The actual timing of these milestones can vary dramatically compared to our estimates, in some cases for reasons beyond our control. If we do not meet these milestones as publicly announced, or at all, the commercialization of our product candidates may be delayed or never achieved and, as a result, our stock price may decline. Additionally, delays relative to our projected timelines are likely to cause overall expenses to increase, which may require us to raise additional capital sooner than expected and prior to achieving targeted development milestones.

Any drug delivery device that we potentially use to deliver our product candidates may have its own regulatory, development, supply and other risks.

We expect to deliver our product candidates via a drug delivery device, such as an injector or other delivery system. There may be unforeseen technical complications related to the development activities required to bring such a product to market, including primary container compatibility and/or dose volume requirements. Our product candidates may not be approved or may be substantially delayed in receiving approval if the devices that we choose to develop do not gain and/or maintain their own regulatory approvals or clearances. Where approval of the drug product and device is sought under a single application, the increased complexity of the review process may delay approval. In addition, some drug delivery devices are provided by single-source unaffiliated third-party companies. We may be dependent on the sustained cooperation and effort of those third-party companies both to supply the devices and, in some cases, to conduct the studies required for approval or other regulatory clearance of the devices. Even if approval is obtained, we may also be dependent on those third-party companies continuing to maintain such approvals or clearances once they have been received. Failure of third-party companies to supply the devices, to successfully complete studies on the devices in a timely manner, or to obtain or maintain required approvals or clearances of the devices could result in increased development costs, delays in or failure to obtain regulatory approval and delays in product candidates reaching the market or in gaining approval or clearance for expanded labels for new indications.

Our approach to the discovery and development of our programs is unproven, and we may not be successful in our efforts to build a pipeline of programs with commercial value.

Our approach to the discovery and development of the research programs with respect to which we have exercised the Option to acquire intellectual property license rights to or have the Option to acquire intellectual property license rights to pursuant to the Paragon Agreement leverages clinically validated mechanisms of action and incorporates advanced antibody engineering to optimize half-life and other properties designed to overcome limitations of existing therapies. Our programs are purposefully designed to improve upon existing product candidates and products while maintaining the same, well-established mechanisms of action. However, the scientific research that forms the basis of our efforts to develop programs using half-life extension technologies, including YTE and LS amino acid substitutions, is ongoing and may not result in viable programs. We have limited clinical data on product candidates utilizing YTE and LS half-life extension technologies, especially in I&I indications, demonstrating whether they are safe or effective for long-term treatment in humans. The long-term safety and efficacy of these technologies and the extended half-life and exposure profile of our programs compared to currently approved products is unknown.

We may ultimately discover that utilizing half-life extension technologies for our specific targets and indications and any programs resulting therefrom do not possess certain properties required for therapeutic effectiveness. We currently have only preclinical data regarding the increased half-life properties of our programs and the same results may not be seen in humans. In addition, programs using half-life extension technologies may demonstrate different chemical and pharmacological properties in participants than they do in laboratory studies. This technology and any programs resulting therefrom may not demonstrate the same chemical and pharmacological properties in humans and may interact with human biological systems in unforeseen, ineffective or harmful ways.

In addition, we may in the future seek to discover and develop programs that are based on novel targets and technologies that are unproven. If our discovery activities fail to identify novel targets or technologies for drug discovery, or such targets prove to be unsuitable for treating human disease, we may not be able to develop viable additional programs. We and our existing or future collaborators may never receive approval to market and commercialize any product candidate. Even if we or an existing or future collaborator obtains regulatory approval, the approval may be for targets, disease indications or patient populations that are not as broad as we intended or desired or may require labeling that includes significant use or distribution restrictions or safety warnings. If the products resulting from the research programs with respect to which we have exercised the Option to acquire intellectual property license rights to or have the Option to acquire intellectual property license rights to pursuant to the Paragon Agreement prove to be ineffective, unsafe or commercially unviable, such programs would have little, if any, value, which would have a material and adverse effect on our business, financial condition, results of operations and prospects.

Preclinical and clinical development involves a lengthy and expensive process that is subject to delays and with uncertain outcomes, and results of earlier studies and trials may not be predictive of future clinical trial results. If our preclinical studies and clinical trials are not sufficient to support regulatory approval of any of our product candidates, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development of such product candidate.

Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete preclinical studies and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidate in humans. Our clinical trials may not be conducted as planned or completed on schedule, if at all, and failure can occur at any time during the preclinical study or clinical trial process. For example, we depend on the availability of NHPs to conduct certain preclinical studies that we are required to complete prior to submitting an IND and initiating clinical development. There is currently a global shortage of NHPs available for drug development. This could cause the cost of obtaining NHPs for our future preclinical studies to increase significantly and, if the shortage continues, could also result in delays to our development timelines.

Furthermore, a failure of one or more clinical trials can occur at any stage of testing. The outcome of preclinical studies and early-stage clinical trials may not be predictive of the success of later clinical trials. 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 product candidates. In addition, we expect to rely on participants to provide feedback on measures such as measures of quality of life, which are subjective and inherently difficult to evaluate. These measures can be influenced by factors outside of our control, and can vary widely from day to day for a particular participant, and from participant to participant and from site to site within a clinical trial.

We cannot be sure that the FDA will agree with our clinical development plan. We plan to use the data from our planned Phase 1 trials of our SPY001 and SPY002 programs in healthy volunteers to support Phase 2 trials in IBD and other I&I indications. If the FDA requires us to conduct additional trials or enroll additional participants, our development timelines may be delayed. We cannot be sure that submission of an IND, BLA or similar application will result in the FDA or comparable foreign regulatory authorities, as applicable, allowing clinical trials to begin in a timely manner, if at all. Moreover, even if these trials begin, issues may arise that could cause regulatory authorities to suspend or terminate such clinical trials. Events that may prevent successful or timely initiation or completion of clinical trials include: inability to generate sufficient preclinical, toxicology or other in vivo or in vitro data to support the initiation or continuation of clinical trials; delays in reaching a consensus with regulatory authorities on study design or implementation of the clinical trials; delays or failure in obtaining regulatory authorization to commence a trial; delays in reaching agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and clinical trial sites; delays in identifying, recruiting and training suitable clinical investigators; delays in obtaining required IRB approval at each clinical trial site; delays in manufacturing, testing, releasing, validating or importing/exporting sufficient stable quantities of our product candidates for use in clinical trials or the inability to do any of the foregoing; failure by our CROs, other third parties or us to adhere to clinical trial protocols; failure to perform in accordance with the FDA's or any other regulatory authority's good clinical practice requirements ("GCPs") or applicable regulatory guidelines in other countries; changes to the clinical trial protocols; clinical sites deviating from trial protocol or dropping out of a trial; changes in regulatory requirements and guidance that require amending or submitting new clinical protocols; selection of clinical endpoints that require prolonged periods of observation or analyses of resulting data; transfer of manufacturing processes to facilities operated by a contract manufacturing organization

("CMO") and delays or failure by our CMOs or us to make any necessary changes to such manufacturing process; and third parties being unwilling or unable to satisfy their contractual obligations to us.

We could also encounter delays if a clinical trial is suspended or terminated by us, by the IRBs of the institutions in which such clinical trials are being conducted, by the Data Safety Monitoring Board, if any, for such clinical trial or by the FDA or comparable foreign regulatory authorities. Such authorities may suspend or terminate a clinical trial due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical trial protocols, inspection of the clinical trial operations or trial site by the FDA or comparable foreign regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from the programs, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. 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, if the results of these trials are not positive or are only moderately positive or if there are safety concerns, our business and results of operations may be adversely affected and we may incur significant additional costs.

We are researching the potential use of complementary diagnostics in connection with the development of our product candidates, and although we do not currently anticipate such diagnostics would be required for the regulatory approval of any of our product candidates, they may be helpful to maximize the clinical and commercial success of our product candidates and if we fail to develop such complementary diagnostics or obtain regulatory approvals that may be required if they will be used commercially alongside any of our product candidates, our products may not be as competitive or commercially successful as they could be.

A complementary diagnostic is a medical device, often an in vitro device, which provides information that is valuable for the safe and effective use of a corresponding therapeutic drug or biologic product. A complementary diagnostic can be used to identify patients or subsets of patients who are most likely to benefit from the therapeutic product.

A complementary diagnostic is generally developed in conjunction with the clinical program for an associated therapeutic product. The development path of a complementary diagnostic may include additional meetings with regulatory authorities, such as a pre-submission meeting and the requirement to submit an investigational device exemption application. In the case of a complementary diagnostic that is designated as “significant risk device,” approval of an investigational device exemption by the FDA and IRB is required before such diagnostic is used in conjunction with the clinical trials for a corresponding product candidate.

To be successful in developing, validating, obtaining approval of and commercializing a complementary diagnostic, we or our collaborators will need to address a number of scientific, technical, regulatory and logistical challenges. We have no prior experience with medical device or diagnostic test development. If we choose to develop and seek FDA approval for complementary diagnostic tests on our own, we may require additional personnel. We may rely on third parties for the design, development, testing, validation and manufacture of complementary diagnostic tests for our therapeutic product candidates that may benefit from such tests, the application for and receipt of any required regulatory approvals, and the commercial supply of these complementary diagnostics.

Although we currently plan to focus our complementary diagnostic development program on diagnostics that may help to identity high/better responding patients for our product candidates, we do not believe such complementary diagnostics will be required by regulatory authorities in connection with granting regulatory approval for our product candidates but may aid in clinical trial recruitment, post-approval treatment decisions and maximizing the commercial success of our product candidates. If we or third parties we engage are unable to successfully develop complementary diagnostics for our product candidates, or experience delays in doing so:

- we may be unable to maximize our potential to identify appropriate patients for enrollment in our clinical trials, which may adversely affect the development of our therapeutic product candidates;

- if the FDA or other regulators determine that the safe and effective use of our therapeutic product candidates, if any, depends on the complementary diagnostics we develop then we would have to expend time and resources to obtain regulatory approval of such complementary diagnostics which could cause delays in the commercial launch or success of our product candidates; and

- we may not realize the full commercial potential of any therapeutics that receive marketing approval.

As a result of any of these events, our business, financial condition, results of operations and prospects could be materially and adversely affected.

We have limited experience in developing and commercializing diagnostics and have never applied for or obtained regulatory clearance or approval for any diagnostic tests.

To be successful in developing and commercializing therapeutic product candidates in combination with diagnostic candidates, we will need to address a number of scientific, technical, regulatory and logistical challenges. We currently anticipate that we or a collaborator may need to obtain marketing authorization from the FDA in order to legally market such diagnostics in the United States. As a company, we have little experience in the development of diagnostic tests and may not be successful in developing appropriate diagnostics to pair with any of our therapeutic product candidates that receive marketing approval, and have never applied for or obtained regulatory clearance or approval of any such diagnostic tests. Given our limited experience in developing diagnostic tests, we may rely in part or in whole on third parties for their design, development and manufacture of such tests.

Before a new medical device, or a new intended use of, claim for, or significant modification to an existing device, can be marketed in the United States, a company must first submit an application for and receive 510(k) clearance pursuant to a premarket notification submitted under Section 510(k) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), de-novo classification, or PMA approval from FDA, unless an exemption applies. The PMA approval pathway, which we expect to pursue for our complementary diagnostic product candidates, requires an applicant to demonstrate the safety and effectiveness of the product based, in part, on valid scientific evidence, including, but not limited to, technical, preclinical, and clinical data. The 510(k) pathway requires a FDA finding that the test is substantially equivalent to a legally marketed predicate device. If no legally marketed predicate can be identified to enable use of the 510(k) pathway, the device is automatically classified under the FDCA into Class III, which generally requires PMA approval. However, for low- to moderate-risk novel devices, FDA allows for the possibility of marketing authorization through the "de novo classification" process rather than requiring the device to be subject to PMA approval. Products that are approved through a PMA application generally need prior FDA approval before modifications can be made that affect safety or effectiveness, and certain modifications to a 510(k)-cleared device may also require FDA premarket review before the modified product can be marketed. If we are unable to successfully develop, obtain regulatory clearance for and commercialize diagnostics to pair with our therapeutic product candidates, it could adversely impact our ability to develop and generate revenue from our product candidates.

Additional time may be required to obtain regulatory approval for our product candidates and future product candidates because of their status as combination products.

We may pursue development of combination products that require coordination within the FDA and comparable foreign regulatory authorities for review of its device and biologic components. Although the FDA and comparable foreign regulatory authorities have systems in place for the review and approval of combination products such as ours, we may experience delays in the development and commercialization of our product candidates due to regulatory timing constraints and uncertainties in the product development and approval process. Of note, prior clearance or approval of one component of a combination product does not increase the likelihood that FDA will approve a later product combining the previously cleared product or approved active ingredient with a novel active ingredient.

If we encounter difficulties enrolling participants in our future clinical trials, our clinical development activities could be delayed or otherwise adversely affected.

We may experience difficulties in patient participant enrollment in our future clinical trials for a variety of reasons. The timely completion of clinical trials in accordance with their protocols depends, among other things, on our ability to enroll a sufficient number of participants who remain in the trial until its conclusion. The enrollment of participants in future trials for any of our programs will depend on many factors, including if participants choose to enroll in clinical trials, rather than using approved products, or if our competitors have ongoing clinical trials for programs that are under development for the same indications as our programs, and participants instead enroll in such clinical trials. Additionally, the number of participants required for clinical trials of our programs may be larger than we anticipate, especially if regulatory bodies require the completion of non-inferiority or superiority trials. Even if we are able to enroll a sufficient number of participants for our future

clinical trials, we may have difficulty maintaining participants in our clinical trials. Our inability to enroll or maintain a sufficient number of participants would result in significant delays in completing clinical trials or receipt of marketing approvals and increased development costs or may require us to abandon one or more clinical trials altogether.

Preliminary, "topline" or interim data from our clinical trials that we announce or publish from time to time may change as more participant data become available and are subject to audit and verification procedures.

From time to time, we may publicly disclose preliminary or topline data from our preclinical studies and clinical trials, which are based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data. We also make assumptions, estimations, calculations and conclusions as part of our analyses of these data without the opportunity to fully and carefully evaluate complete data. As a result, the preliminary or topline results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated or subsequently made subject to audit and verification procedures.

Any preliminary or topline data should be viewed with caution until the final data are available. From time to time, we may also disclose interim data from our preclinical studies and clinical trials. Interim data are subject to the risk that one or more of the clinical outcomes may materially change as participant enrollment continues and more participant data become available or as participants from our clinical trials continue other treatments. Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular product candidate, the approvability or commercialization of the particular product candidate and our company in general. In addition, the information we choose to publicly disclose regarding a particular preclinical study or clinical trial is based on what is typically extensive information, and you or others may not agree with what we determine is material or otherwise appropriate information to include in our disclosure. If the preliminary, topline or interim data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, our product candidates may be harmed, which could harm our business, operating results, prospects or financial condition.

Our future clinical trials or those of our future collaborators may reveal significant adverse events or undesirable side effects not seen in our preclinical studies and may result in a safety profile that could halt clinical development, inhibit regulatory approval or limit commercial potential or market acceptance of any of our product candidates.

Results of our clinical trials could reveal a high and unacceptable severity and prevalence of side effects, adverse events or unexpected characteristics. While our preclinical studies in NHPs have not shown any such characteristics to date, we have not yet initiated any clinical trials in humans. If significant adverse events or other side effects are observed in any of our future clinical trials, we may have difficulty recruiting participants to such trials, participants may drop out of our trials, or we may be required to abandon the trials or our development efforts of one or more programs altogether. We, the FDA or other applicable regulatory authorities, or an IRB, may suspend any clinical trials of any program at any time for various reasons, including a belief that subjects or patients in such trials are being exposed to unacceptable health risks or adverse side effects. Some potential products developed in the biotechnology industry that initially showed therapeutic promise in early-stage studies and trials have later been found to cause side effects that prevented their further development. Other potential products have shown side effects in preclinical studies, which side effects do not present themselves in clinical trials in humans. Even if the side effects do not preclude the product candidate from obtaining or maintaining marketing approval, undesirable side effects may inhibit market acceptance of the approved product due to its tolerability versus other therapies. In addition, an extended half-life could prolong the duration of undesirable side effects, which could also inhibit market acceptance. Treatment-emergent adverse events could also affect participant recruitment or the ability of enrolled subjects to complete our clinical trials or could result in potential product liability claims. Potential side effects associated with our product candidates may not be appropriately recognized or managed by the treating medical staff, as toxicities resulting from our product candidates may not be normally encountered in the general patient population and by medical personnel. Any of these occurrences could harm our business, financial condition, results of operations and prospects significantly.

In addition, even if we successfully advance our product candidates or any future product candidates through clinical trials, such trials will only include a limited number of participants and limited duration of

exposure to our product candidates. As a result, we cannot be assured that adverse effects of our product candidates will not be uncovered when a significantly larger number of participants are exposed to the product candidate after approval. Further, any clinical trials may not be sufficient to determine the effect and safety consequences of using our product candidates over a multi-year period.

If any of the foregoing events occur or if one or more of the research programs with respect to which we have exercised the Option to acquire intellectual property license rights to or have the Option to acquire intellectual property license rights to pursuant to the Paragon Agreement prove to be unsafe, our entire pipeline could be affected, which would have a material adverse effect on our business, financial condition, results of operations and prospects.

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

Because we have limited financial and managerial resources, we focus our research and development efforts on certain selected programs. For example, we are initially focused on our most advanced programs, SPY001 and SPY002. As a result, we may forgo or delay pursuit of opportunities with other programs 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 for specific indications may not yield any commercially viable product candidates. 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.

Any approved products resulting from our current programs or any future program may not achieve adequate market acceptance among clinicians, patients, healthcare third-party payors and others in the medical community necessary for commercial success and we may not generate any future revenue from the sale or licensing of such products.

Even if regulatory approval is obtained for a product candidate resulting from one of our current or future programs, they may not gain market acceptance among physicians, patients, healthcare payors or the medical community. We may not generate or sustain revenue from sales of the product due to factors such as whether the product can be sold at a competitive cost and whether it will otherwise be accepted in the market. There are several approved products and product candidates in later stages of development for the treatment of IBD. However, our programs incorporate advanced antibody engineering to optimize the half-life and formulation of antibodies; to date, no such antibody has been approved by the FDA for the treatment of IBD. Market participants with significant influence over acceptance of new treatments, such as clinicians and third-party payors, may not adopt a biologic that incorporates half-life extension for our targeted indications, and we may not be able to convince the medical community and third-party payors to accept and use, or to provide favorable reimbursement for, any programs developed by us or our existing or future collaborators. An extended half-life may make it more difficult for patients to change treatments and there is a perception that half-life extension could exacerbate side effects, each of which may adversely affect our ability to gain market acceptance. Market acceptance of our product candidates will depend on many factors, including factors that are not within our control.

Sales of medical products also depend on the willingness of clinicians to prescribe the treatment. We cannot predict whether clinicians, clinicians' organizations, hospitals, other healthcare providers, government agencies or private insurers will determine that our product is safe, therapeutically effective, cost effective or less burdensome as compared with competing treatments. If any current or future product candidate is approved but does not achieve an adequate level of acceptance by such parties, we may not generate or derive sufficient revenue from that product candidate and may not become or remain profitable.

Certain of our programs may compete with our other programs, which could negatively impact our business and reduce our future revenue.

We are developing product candidates for the same indication: IBD, and may in the future develop our programs for other I&I indications. Each such program targets a different mechanism of action. However, developing multiple programs for a single indication may negatively impact our business if the programs compete with each other. For example, if multiple programs are conducting clinical trials at the same time, they

could compete for the enrollment of participants. In addition, if multiple product candidates are approved for the same indication, they may compete for market share, which could limit our future revenue.

We plan to conduct clinical trials for programs at sites outside the United States, and the FDA may not accept data from trials conducted in such locations.

We may choose to conduct one or more of our future clinical trials outside the United States. Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of this data is subject to conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and 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. 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 would delay or permanently halt our development of the applicable product candidates. Even if the FDA accepted such data, it could require us to modify our planned clinical trials to receive clearance to initiate such trials in the United States or to continue such trials once initiated.

Further, conducting international clinical trials presents additional risks that may delay completion of our clinical trials. These risks include the failure of enrolled participants in foreign countries to adhere to clinical protocol as a result of differences in healthcare services or cultural customs that could restrict or limit our ability to conduct our clinical trials, the administrative burdens of conducting clinical trials under multiple sets of foreign regulations, foreign exchange fluctuations, diminished protection of intellectual property in some countries, as well as political and economic risks relevant to foreign countries.

Risks Related to Government Regulation

The regulatory approval processes of the FDA and other comparable foreign regulatory authorities are lengthy, time-consuming and inherently unpredictable. If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals for our product candidates, we will not be able to commercialize, or will be delayed in commercializing, our product candidates, and our ability to generate revenue will be materially impaired.

The process of obtaining regulatory approvals, both in the United States and abroad, is unpredictable, expensive and typically takes many years following commencement of clinical trials, 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. We cannot commercialize product candidates in the United States without first obtaining regulatory approval from the FDA. Similarly, we cannot commercialize product candidates outside of the United States without obtaining regulatory approval from comparable foreign regulatory authorities. Before obtaining regulatory approvals for the commercial sale of our product candidates, including our most advanced product candidates, SPY001 and SPY002, we must demonstrate through lengthy, complex and expensive preclinical studies and clinical trials that our product candidates are both safe and effective for each targeted indication. Securing regulatory approval also requires the submission of information about the drug manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. Further, 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. The FDA and comparable foreign regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other data. Our product candidates could be delayed in receiving, or fail to receive, regulatory approval for many reasons, including: the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials; we may be unable to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that a product candidate is safe and effective for its proposed indication; the results of clinical trials may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for approval; serious and unexpected drug-related side effects may be experienced by participants in our clinical trials or by individuals using drugs similar to our product candidates; we may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks; the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical trials; the data collected from clinical trials of our product candidates may not be acceptable or sufficient to support the submission of a BLA or other submission or to obtain regulatory approval in the United States or elsewhere, and we may be required to

conduct additional clinical trials; the FDA or the applicable foreign regulatory authority may disagree regarding the formulation, labeling and/or the specifications of our product candidates; the FDA or comparable foreign regulatory authorities may fail to approve the manufacturing processes or facilities of third-party manufacturers with which we contract for clinical and commercial supplies; and the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

Of the large number of drugs in development, only a small percentage successfully complete the FDA or foreign regulatory approval processes and are commercialized. The lengthy approval process as well as the unpredictability of future clinical trial results may result in our failing to obtain regulatory approval to market our product candidates, which would significantly harm our business, results of operations and prospects.

If we were to obtain approval, regulatory authorities may approve any of our product candidates for fewer or more limited indications than we request, including failing to approve the most commercially promising indications, may grant approval contingent on the performance of costly post-marketing clinical trials, or may approve a product candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals for our product candidates, we will not be able to commercialize, or will be delayed in commercializing, our product candidates and our ability to generate revenue will be materially impaired.

We may not be able to meet requirements for the chemistry, manufacturing and control of our programs.

In order to receive approval of our products by the FDA and comparable foreign regulatory authorities, we must show that we and our contract manufacturing partners are able to characterize, control and manufacture our drug products safely and in accordance with regulatory requirements. This includes manufacturing the active ingredient, developing an acceptable formulation, manufacturing the drug product, performing tests to adequately characterize the formulated product, documenting a repeatable manufacturing process, and demonstrating that our drug products meet stability requirements. Meeting these chemistry, manufacturing and control requirements is a complex task that requires specialized expertise. If we are not able to meet the chemistry, manufacturing and control requirements, we may not be successful in getting our products approved.

Our product candidates for which we intend to seek approval as biologics may face competition sooner than anticipated.

The Patient Protection and Affordable Act, as amended by the Healthcare and Education Reconciliation Act (the “ACA”), includes a subtitle called the Biologics Price Competition and Innovation Act of 2009 (“BPCIA”), which created an abbreviated approval pathway for biological products that are biosimilar to or interchangeable with an FDA-licensed reference biological product. Under the BPCIA, an application for a highly similar or “biosimilar” product may not be submitted to the FDA until four years following the date that the reference product was first approved by the FDA. In addition, the approval of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first approved. During this 12-year period of exclusivity, another company may still market a competing version of the reference product if the FDA approves a full BLA for the competing product containing the sponsor’s own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of their product.

We believe that any of our product candidates approved as biologics under a BLA should qualify for the 12-year period of exclusivity. However, there is a risk that this exclusivity could be shortened due to congressional action or otherwise, or that the FDA will not consider our product candidates to be reference products for competing products, potentially creating the opportunity for competition sooner than anticipated. Other aspects of the BPCIA, some of which may impact the BPCIA exclusivity provisions, have also been the subject of recent litigation. Moreover, the extent to which a biosimilar, once approved, will be substituted for any reference products in a way that is similar to traditional generic substitution for non-biological products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing.

Even if we receive regulatory approval of our product candidates, we will be subject to extensive ongoing regulatory obligations and continued regulatory review, which may result in significant

additional expense and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our product candidates.

Any regulatory approvals that we may receive for our product candidates will require the submission of reports to regulatory authorities and surveillance to monitor the safety and efficacy of the product candidate, may contain significant limitations related to use restrictions for specified age groups, warnings, precautions or contraindications, and may include burdensome post-approval study or risk management requirements. For example, the FDA may require a risk evaluation and mitigation strategy ("REMS") in order to approve our product candidates, which could entail requirements for a medication guide, physician training and communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. In addition, if the FDA or comparable foreign regulatory authorities approve our product candidates, our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale, distribution, import and export will be subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by comparable foreign regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as on-going compliance with current cGMPs and GCPs for any clinical trials that we conduct following approval. In addition, manufacturers of drug products and their facilities are subject to continual review and periodic, unannounced inspections by the FDA and other regulatory authorities for compliance with cGMPs.

If we or a regulatory authority discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facilities where the product is manufactured, a regulatory authority may impose restrictions on that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing. restrictions on our ability to conduct clinical trials, including full or partial clinical holds on ongoing or planned trials, restrictions on the manufacturing process, warning or untitled letters, civil and criminal penalties, injunctions, product seizures, detentions or import bans, voluntary or mandatory publicity requirements and imposition of restrictions on operations, including costly new manufacturing requirements. The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and generate revenue and could require us to expend significant time and resources in response and could generate negative publicity.

We may face difficulties from healthcare legislative reform measures.

Existing regulatory policies may change, and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability. See the section titled “Business – Government Regulation – Healthcare Reform” for a more detailed description of healthcare reform measures that may prevent us from being able to generate revenue, attain profitability, or commercialize our product candidates.

Our business operations and current and future arrangements with investigators, healthcare professionals, consultants, third-party payors, patient organizations and customers will be subject to applicable healthcare regulatory laws, which could expose us to penalties.

Our business operations and current and future arrangements with investigators, healthcare professionals, consultants, third-party payors, patient organizations and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations. These laws may constrain the business or financial arrangements and relationships through which we conduct our operations, including how we research, market, sell and distribute our product candidates, if approved. See the section titled “Business – Government Regulation – Other Healthcare Laws and Compliance Requirements” for a more detailed description of the laws that may affect our ability to operate.

Ensuring that our internal operations and future business arrangements with third parties comply with applicable healthcare laws and regulations will involve substantial costs. If our operations are found to be in violation of any of these laws or any other governmental laws and regulations that may apply to us, we may be subject to significant penalties, including civil, criminal and administrative penalties, damages, fines, exclusion

from government-funded healthcare programs, integrity oversight and reporting obligations to resolve allegations of non-compliance, disgorgement, individual imprisonment, contractual damages, reputational harm, diminished profits and the curtailment or restructuring of our operations. Further, defending against any such actions can be costly and time-consuming and may require significant personnel resources. Therefore, even if we are successful in defending against any such actions that may be brought against us, our business may be impaired.

Even if we are able to commercialize any product candidates, due to unfavorable pricing regulations and/or third-party coverage and reimbursement policies, we may not be able to offer such product candidates at competitive prices which would seriously harm our business.

We intend to seek approval to market our product candidates in both the United States and in selected foreign jurisdictions. If we obtain approval in one or more foreign jurisdictions for our product candidates, we will be subject to rules and regulations in those jurisdictions. Our ability to successfully commercialize any product candidates that we may develop will depend in part on the extent to which reimbursement for these product candidates and related treatments will be available from government health administration authorities, private health insurers and other organizations. Government authorities and other third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. These entities may create preferential access policies for a competitor's product, including a branded or generic/biosimilar product, over our products in an attempt to reduce their costs, which may reduce our commercial opportunity. Additionally, if any of our product candidates are approved and we are found to have improperly promoted off-label uses of those product candidates, we may become subject to significant liability, which would materially adversely affect our business and financial condition. See the sections titled "Business – Government Regulation – Coverage and Reimbursement" and "Business – Other Government Regulation Outside of the United States – Regulation in the European Union" for a more detailed description of the government regulations and third party payor practices that may affect our ability to commercialize our product candidates.

We are subject to U.S. and certain foreign export and import controls, sanctions, embargoes, anti-corruption laws, and anti-money laundering laws and regulations. We can face criminal liability and other serious consequences for violations, which can harm our business.

We are subject to export control and import laws and regulations, including the U.S. Export Administration Regulations, U.S. Customs regulations, various economic and trade sanctions regulations administered by the U.S. Treasury Department's Office of Foreign Assets Controls, the U.S. Foreign Corrupt Practices Act of 1977, as amended, the U.S. domestic bribery statute contained in 18 U.S.C. § 201, the U.S. Travel Act, the USA PATRIOT Act, and other state and national anti-bribery and anti-money laundering laws in the countries in which we conduct activities. Anti-corruption laws are interpreted broadly and prohibit companies and their employees, agents, contractors, and other collaborators from authorizing, promising, offering, or providing, directly or indirectly, improper payments or anything else of value to or from recipients in the public or private sector. We may engage third parties to sell our products outside the United States, to conduct clinical trials, and/or to obtain necessary permits, licenses, patent registrations, and other regulatory approvals. We have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. We can be held liable for the corrupt or other illegal activities of our employees, agents, contractors, and other collaborators, even if we do not explicitly authorize or have actual knowledge of such activities. Any violations of the laws and regulations described above may result in substantial civil and criminal fines and penalties, imprisonment, the loss of export or import privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm, and other consequences.

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

In some countries, particularly member states of the EU, the pricing of prescription drugs is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after receipt of marketing approval for a therapeutic. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. 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 distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices. To obtain coverage and reimbursement or pricing approvals in some countries, we or current or future collaborators may be required to conduct a clinical trial or other studies that compare the cost-effectiveness of our product candidates to other available therapies in order to obtain or maintain reimbursement or pricing approval. Publication of discounts by third-party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If reimbursement of any product candidate approved for marketing is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business, financial condition, results of operations or prospects could be materially and adversely affected. Brexit could lead to legal uncertainty and potentially divergent national laws and regulations, including those related to the pricing of prescription pharmaceuticals, as the UK determines which EU laws to replicate or replace. If the UK were to significantly alter its regulations affecting the pricing of prescription pharmaceuticals, we could face significant new costs.

A breakthrough therapy, fast track, or other expedited designation for our product candidates may not lead to a faster development or regulatory review or approval process, and it does not increase the likelihood that those product candidates will receive marketing approval.

We may seek a breakthrough therapy, fast track, or other designation for appropriate product candidates. Designations such as these are within the discretion of the FDA, or other comparable regulatory authorities. The receipt of a designation for a product candidate may not result in a faster development process, review or approval compared to products considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify under one of FDA's designation programs, 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. See the section titled "Business – Government Regulation – Expedited Development and Review Programs" for a more detailed description of the process for seeking expedited designations such as fast track or breakthrough therapy designations.

Risks Related to Our Intellectual Property

Our ability to obtain and protect our patents and other proprietary rights is uncertain, exposing us to the possible loss of competitive advantage.

We rely upon a combination of patents, trademarks, trade secret protection, confidentiality agreements and the Paragon Agreement to protect the intellectual property related to our programs and technologies and to prevent third parties from competing unfairly with us. Our success depends in large part on our ability to obtain and maintain patent protection for our platform technologies, programs and their uses, as well as our ability to operate without infringing on or violating the proprietary rights of others. We own and have licensed rights to pending patent applications and expect to continue to file patent applications in the United States and abroad related to our novel discoveries and technologies that are important to our business. However, we may not be able to protect our intellectual property rights throughout the world and the legal systems in certain countries may not favor enforcement or protection of patents, trade secrets and other intellectual property. Filing, prosecuting and defending patents on programs worldwide would be expensive and our intellectual property rights in some foreign jurisdictions can be less extensive than those in the United States; the reverse may also occur. As such, we may not have patents in all countries or all major markets and may not be able to obtain patents in all jurisdictions even if we apply for them. Our competitors may operate in countries where we do not have patent protection and can freely use our technologies and discoveries in such countries to the extent such technologies and discoveries are publicly known or disclosed in countries where we do have patent protection or pending patent applications.

Our pending and future patent applications may not result in patents being issued. Any issued patents may not afford sufficient protection of our programs or their intended uses against competitors, nor can there be any assurance that the patents issued will not be infringed, designed around, invalidated by third parties, or effectively prevent others from commercializing competitive technologies, products or programs. Even if these patents are granted, they may be difficult to enforce. Further, any issued patents that we may license or own covering our programs could be narrowed or found invalid or unenforceable if challenged in court or before administrative bodies in the United States or abroad, including the United States Patent and Trademark Office ("USPTO"). Further, if we encounter delays in our clinical trials or delays in obtaining regulatory approval, the period of time during which we could market our product candidates under patent protection would be reduced. Thus, the patents that we may own and license may not afford us any meaningful competitive advantage.

In addition to seeking patents for some of our technology and programs, we may also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. Any disclosure, either intentional or unintentional, by our employees, the employees of third parties with whom we share our facilities or third-party consultants and vendors that we engage to perform research, clinical trials or manufacturing activities, or misappropriation by third parties (such as through a cybersecurity breach) of our trade secrets or proprietary information could enable competitors to duplicate or surpass our technological achievements, thus eroding our competitive position in our market. In order to protect our proprietary technology and processes, we rely in part on confidentiality agreements with our collaborators, employees, consultants, outside scientific collaborators and sponsored researchers and other advisors. These agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. We may need to share our proprietary information, including trade secrets, with future business partners, collaborators, contractors and others located in countries at heightened risk of theft of trade secrets, including through direct intrusion by private parties or state actors and those affiliated with or controlled by state actors. In addition, while we undertake efforts to protect our trade secrets and other confidential information from disclosure, others may independently discover trade secrets and proprietary information, and in such cases, we may not be able to assert any trade secret rights against such party. Costly and time-consuming litigation could be necessary to enforce and determine the scope of our proprietary rights and failure to obtain or maintain trade secret protection could adversely affect our competitive business position.

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

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

Because our development programs currently do and may in the future require the use of proprietary rights held by third parties, the growth of our business may depend in part on our ability to acquire, in-license, or use these third-party proprietary rights. We may be unable to acquire or in-license any compositions, methods of use, processes or other third-party intellectual property rights from third parties that we identify as necessary for our programs. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies may pursue strategies to license or acquire third-party intellectual property rights that we may consider attractive or necessary. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment or at all. If we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we do obtain, we may have to abandon development of the relevant program, which could have a material adverse effect on our business, financial condition, results of operations, and prospects.

While we normally seek to obtain the right to control prosecution, maintenance and enforcement of the patents relating to our programs, there may be times when the filing and prosecution activities for patents and patent applications relating to our programs are controlled by our current and future licensors or collaboration partners. If any of our current and future licensors or collaboration partners fail to prosecute, maintain and enforce such patents and patent applications in a manner consistent with the best interests of our business, including by payment of all applicable fees for patents covering our product candidates, we could lose our rights to the intellectual property or our exclusivity with respect to those rights, our ability to develop and commercialize those product candidates may be adversely affected and we may not be able to prevent competitors from making, using and selling competing products. In addition, even where we have the right to control patent prosecution of patents and patent applications we have licensed to and from third parties, we may still be adversely affected or prejudiced by actions or inactions of our licensees, our current and future licensors and their counsel that took place prior to the date upon which we assumed control over patent prosecution.

Our current and future licensors may rely on third-party consultants or collaborators or on funds from third parties such that our current and future licensors are not the sole and exclusive owners of the patents we in-license. If other third parties have ownership rights to our current and future in-licensed patents, 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.

It is possible that we may be unable to obtain licenses at a reasonable cost or on reasonable terms, if at all. 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. In that event, we may be required to expend significant time and resources to redesign our technology, programs, 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 product candidates, which could harm our business, financial condition, results of operations, and prospects significantly. We cannot provide any assurances that third-party patents do not exist which might be enforced against our current technology, manufacturing methods, programs, or future methods or products resulting in either an injunction prohibiting our manufacture or future sales, or, with respect to our future sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties, which could be significant.

Disputes may arise between us and our current and future licensors regarding intellectual property subject to a license agreement, including: the scope of rights granted under the license agreement and other interpretation-related issues; whether and the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement; our right to sublicense patents and other rights to third parties; our right to transfer or assign the license; the inventorship and ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our current and future licensors and us and our partners; and the priority of invention of patented technology.

We may be subject to patent infringement claims or may need to file claims to protect our intellectual property, which could result in substantial costs and liability and prevent us from commercializing our potential products.

Because the intellectual property landscape in the biotechnology industry is rapidly evolving and interdisciplinary, it is difficult to conclusively assess our freedom to operate and guarantee that we can operate without infringing on or violating third party rights. If certain of our product candidates are ultimately granted regulatory approval, patent rights held by third parties, if found to be valid and enforceable, could be alleged to render one or more of our product candidates infringing. If a third party successfully brings a claim against us, we may be required to pay substantial damages, be forced to abandon any affected product candidate and/or seek a license from the patent holder. In addition, any intellectual property claims (e.g. patent infringement or trade secret theft) brought against us, whether or not successful, may cause us to incur significant legal expenses and divert the attention of our management and key personnel from other business concerns. We cannot be certain that patents owned or licensed by us will not be challenged by others in the course of litigation. Some of our competitors may be able to sustain the costs of complex intellectual property litigation more effectively than we can because they have substantially greater resources. In addition, any uncertainties resulting from the initiation and continuation of any litigation could have a material adverse effect on our ability to raise funds and on the market price of our common stock.

Competitors may infringe or otherwise violate our patents, trademarks, copyrights or other intellectual property. To counter infringement or other violations, we may be required to file claims, which can be expensive and time-consuming. Any such claims could provoke these parties to assert counterclaims against us, including claims alleging that we infringe their patents or other intellectual property rights. In addition, in a patent infringement proceeding, a court or administrative body may decide that one or more of the patents we assert is invalid or unenforceable, in whole or in part, construe the patent's claims narrowly or refuse to prevent the other party from using the technology at issue on the grounds that our patents do not cover the technology. Similarly, if we assert trademark infringement claims, a court or administrative body may determine that the marks we have asserted are invalid or unenforceable or that the party against whom we have asserted trademark infringement has superior rights to the marks in question. In such a case, we could ultimately be forced to cease use of such marks. In any intellectual property litigation, even if we are successful, any award of monetary damages or other remedy we receive may not be commercially valuable.

Further, we may be required to protect our patents through procedures created to attack the validity of a patent at the USPTO. An adverse determination in any such submission or proceeding could reduce the scope or enforceability of, or invalidate, our patent rights, which could adversely affect our competitive position. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in United States federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action.

In addition, if our programs are found to infringe the intellectual property rights of third parties, these third parties may assert infringement claims against our future licensees and other parties with whom we have business relationships and we may be required to indemnify those parties for any damages they suffer as a result of these claims, which may require us to initiate or defend protracted and costly litigation on behalf of licensees and other parties regardless of the merits of such claims. If any of these claims succeed, we may be

forced to pay damages on behalf of those parties or may be required to obtain licenses for the products they use.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation or other legal proceedings relating to our intellectual property rights, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation or other proceedings.

We may be subject to claims that we have wrongfully hired an employee from a competitor or that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties.

As is common in the biotechnology industry, in addition to our employees, we engage the services of consultants to assist us in the development of our programs. Many of these consultants, and many of our employees, were previously employed at, or may have previously provided or may be currently providing consulting services to, other biotechnology or pharmaceutical companies including our competitors or potential competitors. We could in the future be subject to claims that we or our employees have inadvertently or otherwise used or disclosed alleged trade secrets or other confidential information of former employers or competitors. Although we try to ensure that our employees and consultants do not use the intellectual property, proprietary information, know-how or trade secrets of others in their work for us, we may become subject to claims that we caused an employee to breach the terms of his or her non-competition or non-solicitation agreement, or that we or these individuals have, inadvertently or otherwise, used or disclosed the alleged trade secrets or other proprietary information of a former employer or competitor.

While we may litigate to defend ourselves against these claims, even if we are successful, litigation could result in substantial costs and could be a distraction to management. If our defenses to these claims fail, in addition to requiring us to pay monetary damages, a court could prohibit us from using technologies or features that are essential to our programs, if such technologies or features are found to incorporate or be derived from the trade secrets or other proprietary information of the former employers. Moreover, any such litigation or the threat thereof may adversely affect our reputation, our ability to form strategic alliances or sublicense our rights to collaborators, engage with scientific advisors or hire employees or consultants, each of which would have an adverse effect on our business, results of operations and financial condition. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

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 (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. U.S. Supreme Court and U.S. Court of Appeals for the Federal Circuit rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations, including in the antibody arts. For example, the United States Supreme Court in *Amgen, Inc. v. Sanofi (Amgen)* recently held that Amgen’s patent claims to a class of

antibodies functionally defined by their ability to bind a particular antigen were invalid for lack of enablement where the patent specification provided twenty-six exemplary antibodies, but the claimed class of antibodies covered a "vast number" of additional antibodies not disclosed in the specification. The Court stated that if patent claims are directed to an entire class of compositions of matter, then the patent specification must enable a person skilled in the art to make and use the entire class of compositions. This decision makes it unlikely that we will be granted U.S. patents with composition of matter claims directed to antibodies functionally defined by their ability to bind a particular antigen. Even if we are granted claims directed to functionally defined antibodies, it is possible that a third party may challenge our patents, when issued, relying on the reasoning in *Amgen* or other recent precedential court decisions. Additionally, there have been proposals for additional changes to the patent laws of the United States and other countries that, if adopted, could impact our ability to enforce our proprietary technology. 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.

Geopolitical instability in the United States and in foreign countries could increase the uncertainties and costs surrounding the prosecution or maintenance of patent applications and the maintenance, enforcement or defense of issued patents. For example, the United States and foreign government actions related to Russia's invasion of Ukraine may limit or prevent filing, prosecution and maintenance of patent applications in Russia. Government actions may also prevent maintenance of issued patents in Russia. These actions could result in abandonment or lapse of patents or patent applications, resulting in partial or complete loss of patent rights in Russia. If such an event were to occur, it could have a material adverse effect on our business. In addition, a decree was adopted by the Russian government in March 2022, allowing Russian companies and individuals to exploit inventions owned by patentees that have citizenship or nationality in, are registered in, or have predominately primary place of business or profit-making activities in the United States and other countries that Russia has deemed unfriendly without consent or compensation. Consequently, we would not be able to prevent third parties from practicing our inventions in Russia or from selling or importing products made using our inventions in and into Russia. Accordingly, our competitive position may be impaired, and our business, financial condition, results of operations and prospects may be adversely affected. In addition, a European Unified Patent Court ("UPC") entered into force on June 1, 2023. The UPC is a common patent court that hears patent infringement and revocation proceedings effective for member states of the EU. This could enable third parties to seek revocation of a European patent in a single proceeding at the UPC rather than through multiple proceedings in each of the jurisdictions in which the European patent is validated. Although we do not currently own any European patents or applications, if we obtain such patents and applications in the future, any such revocation and loss of patent protection could have a material adverse impact on our business and our ability to commercialize or license our technology and products. Moreover, the controlling laws and regulations of the UPC will develop over time, and may adversely affect our ability to enforce or defend the validity of any European patents we may obtain. We may decide to opt out from the UPC any future European patent applications that we may file and any patents we may obtain. If certain formalities and requirements are not met, however, such European patents and patent applications could be challenged for non-compliance and brought under the jurisdiction of the UPC. We cannot be certain that future European patents and patent applications will avoid falling under the jurisdiction of the UPC, if we decide to opt out of the UPC.

Obtaining and maintaining patent protection depends on compliance with various procedural, document submissions, 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 fees, renewal fees, annuities fees and various other governmental fees on patents and/or patent applications are due to be paid to the USPTO and foreign patent agencies in several stages over the lifetime of the patent and/or patent application. The USPTO and various foreign governmental patent agencies also require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. 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, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we fail to maintain the patents and patent applications covering our programs, our competitive position would be adversely affected.

We may not identify relevant third-party patents or may incorrectly interpret the relevance, scope or expiration of a third-party patent, which might adversely affect our ability to develop and market our products.

We cannot guarantee that any of our patent searches or analyses, including the identification of relevant patents, the scope of patent claims or the expiration of relevant patents, are complete or thorough, nor can we be certain that we have identified each and every third-party patent and pending application in the United States and abroad that is relevant to or necessary for the commercialization of our product candidates in any jurisdiction. The scope of a patent claim is determined by an interpretation of the law, the written disclosure in a patent and the patent's prosecution history. Our interpretation of the relevance or the scope of a patent or a pending application may be incorrect. For example, we may incorrectly determine that our products are not covered by a third-party patent or may incorrectly predict whether a third-party's pending application will issue with claims of relevant scope. Our determination of the expiration date of any patent in the United States or abroad that we consider relevant may be incorrect. Our failure to identify and correctly interpret relevant patents may negatively impact our ability to develop and market our products.

In addition, because some patent applications in the United States may be maintained in secrecy until the patents are issued, patent applications in the United States and many foreign jurisdictions are typically not published until 18 months after filing, and publications in the scientific literature often lag behind actual discoveries, we cannot be certain that others have not filed patent applications for technology covered by our issued patents or our pending applications, or that we were the first to invent the technology. Our competitors may have filed, and may in the future file, patent applications covering our products or technology similar to ours. Any such patent application may have priority over our patent applications or patents, which could require us to obtain rights to issued patents covering such technologies.

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

We may be subject to claims that former employees, collaborators or other third parties have an interest in our patents or other intellectual property as an inventor or co-inventor. The failure to name the proper inventors on a patent application can result in the patents issuing thereon being unenforceable. Inventorship disputes may arise from conflicting views regarding the contributions of different individuals named as inventors, the effects of foreign laws where foreign nationals are involved in the development of the subject matter of the patent, conflicting obligations of third parties involved in developing our programs or as a result of questions regarding co-ownership of potential joint inventions. Litigation may be necessary to resolve these and other claims challenging inventorship and/or ownership. Alternatively, or additionally, we may enter into agreements to clarify the scope of our rights in such intellectual property. If we 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, valuable intellectual property. Such an outcome could have a material adverse effect on our business. 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.

Our current and future licensors may have relied on third-party consultants or collaborators or on funds from third parties, such as the U.S. government, such that our licensors are not the sole and exclusive owners of the patents we in-licensed. For example, certain intellectual property we license from the University of Texas at Austin includes inventions that were made with U.S. government support. The U.S. government therefore has certain rights in such inventions under the applicable funding agreements and under applicable law. If other third parties have ownership rights or other rights to our in-licensed patents, 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.

Patent terms may be inadequate to protect the competitive position of 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 United States 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 product candidates might expire before or shortly after such product 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.

Our technology licensed from various third parties may be subject to retained rights.

Our current or future licensors may retain certain rights under the relevant agreements with us, including the right to use the underlying technology for noncommercial academic and research use, to publish general scientific findings from research related to the technology, and to make customary scientific and scholarly disclosures of information relating to the technology. It is difficult to monitor whether our licensors limit their use of the technology to these uses, and we could incur substantial expenses to enforce our rights to our licensed technology in the event of misuse.

Risks Related to Our Reliance on Third Parties

We rely on collaborations and licensing arrangements with third parties, including our arrangement with Paragon. If we are unable to maintain these collaborations or licensing arrangements, or if these collaborations or licensing arrangements are not successful, our business could be negatively impacted.

We currently rely on our collaborations and licensing arrangements with third parties, including Paragon, for a substantial portion of our discovery capabilities and in-licenses.

Collaborations or licensing arrangements that we enter into may not be successful, and any success will depend heavily on the efforts and activities of such collaborators or licensors. If any of our collaborators or licensors experiences delays in performance of, or fails to perform its obligations under their agreement with us, disagrees with our interpretation of the terms of such agreement or terminates their agreement with us, the research programs with respect to which we have exercised the Option to acquire intellectual property license rights to or have the Option to acquire intellectual property license rights to pursuant to the Paragon Agreement and development timeline could be adversely affected. If we fail to comply with any of the obligations under our collaborations or license agreements, including payment terms and diligence terms, our collaborators or licensors may have the right to terminate such agreements, in which event we may lose intellectual property rights and may not be able to develop, manufacture, market or sell the products covered by our agreements or may face other penalties under our agreements. Our collaborators and licensors may also fail to properly maintain or defend the intellectual property we have licensed from them, if required by our agreement with them, or even infringe upon, our intellectual property rights, leading to the potential invalidation of our intellectual property or subjecting us to litigation or arbitration, any of which would be time-consuming and expensive and could harm our ability to commercialize our product candidates. In addition, collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our programs 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.

As part of our strategy, we plan to evaluate additional opportunities to enhance our capabilities and expand our development pipeline or provide development or commercialization capabilities that complement our own. We may not realize the benefits of such collaborations, alliances or licensing arrangements. Any of these relationships may require us to incur non-recurring and other charges, increase our near and long-term expenditures, issue securities that dilute our existing stockholders or disrupt our management and business.

We may face significant competition in attracting appropriate collaborators, and more established companies may also be pursuing strategies to license or acquire third-party intellectual property rights that we consider attractive. These 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 upon, among other things, 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. Collaborations are complex and time-consuming to negotiate, document and execute. In addition, consolidation among large pharmaceutical and biotechnology companies has reduced the number of potential future collaborators. We may not be able to negotiate additional collaborations on a timely basis, 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.

We currently rely, and plan to rely in the future, on third parties to conduct and support our preclinical studies and clinical trials. If these third parties do not properly and successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval of or commercialize our product candidates.

We have utilized and plan to continue to utilize and depend upon independent investigators and collaborators, such as medical institutions, CROs, contract testing labs and strategic partners, to conduct and support our preclinical studies and clinical trials under agreements with us. We will rely heavily on these third parties over the course of our preclinical studies and clinical trials, and we control only certain aspects of their activities. As a result, we will have less direct control over the conduct, timing and completion of these preclinical studies and clinical trials and the management of data developed through preclinical studies and clinical trials than would be the case if we were relying entirely upon our own staff. Nevertheless, we are responsible for ensuring that each of our studies and trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on these third parties does not relieve us of our regulatory responsibilities. We and our third-party contractors and CROs are required to comply with GCP regulations, which are regulations and guidelines enforced by the FDA and comparable foreign regulatory authorities for all of our programs in clinical development. If we or any of these third parties fail to comply with applicable GCP regulations, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP regulations. In addition, our clinical trials must be conducted with products produced under cGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. Moreover, our business may be implicated if any of these third parties violates federal or state fraud and abuse or false claims laws and regulations or healthcare privacy and security laws.

Any third parties conducting our clinical trials will not be our employees and, except for remedies available to us under our agreements with such third parties, we cannot control whether they devote sufficient time and resources to our programs. These third parties may be involved in mergers, acquisitions or similar transactions and may have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other product development activities, which could negatively affect their performance on our behalf and the timing thereof and could lead to products that compete directly or indirectly with our current or future product candidates. If these third parties do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to complete development of, obtain regulatory approval of or successfully commercialize our product candidates.

In addition, we currently rely on foreign CROs and CMOs, including WuXi Biologics, and will likely continue to rely on foreign CROs and CMOs in the future. Foreign CMOs may be subject to U.S. legislation, including the proposed BIOSECURE bill, trade restrictions and other foreign regulatory requirements which could increase the cost or reduce the supply of material available to us, delay the procurement or supply of such material or have an adverse effect on our ability to secure significant commitments from governments to purchase our potential therapies.

For example, the biopharmaceutical industry in China is strictly regulated by the Chinese government. Changes to Chinese regulations or government policies affecting biopharmaceutical companies are unpredictable and may have a material adverse effect on our collaborators in China which could have an adverse effect on our business, financial condition, results of operations and prospects. Evolving changes in China's public health, economic, political, and social conditions and the uncertainty around China's relationship with other governments, such as the United States and the UK, could also negatively impact our ability to manufacture our product candidates for our planned clinical trials or have an adverse effect on our ability to secure government funding, which could adversely affect our financial condition and cause us to delay our clinical development programs.

We currently rely and expect to rely in the future on the use of manufacturing suites in third-party facilities or on third parties to manufacture our product candidates, and we may rely on third parties to produce and process our products, if approved. Our business could be adversely affected if we are

unable to use third-party manufacturing suites or if the third-party manufacturers encounter difficulties in production.

We do not currently own any facility that may be used as our clinical or commercial manufacturing and processing facility and must currently rely on CMOs to manufacture our product candidates. We have not yet caused our product candidates to be manufactured on a commercial scale and may not be able to do so for any of our programs, if approved. We currently have a sole source relationship for our supply of the SPY001 program. If there should be any disruption in such supply arrangement, including any adverse events affecting our sole supplier, it could have a negative effect on the clinical development of our programs and other operations while we work to identify and qualify an alternate supply source. We may not control the manufacturing process of, and may be completely dependent on, our contract manufacturing partners for compliance with cGMP requirements and any other regulatory requirements of the FDA or comparable foreign regulatory authorities for the manufacture of our product candidates. Beyond periodic audits, we have limited control over the ability of our CMOs to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any approval in the future, we may need to find alternative manufacturing facilities, which would require the incurrence of significant additional costs, delays, and materially adversely affect our ability to develop, obtain regulatory approval for or market our product candidates, if approved. Similarly, our failure, or the failure of our CMOs, to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or drugs, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates or drugs and harm our business and results of operations.

Moreover, our CMOs may experience manufacturing difficulties due to resource constraints, supply chain issues, or as a result of labor disputes or unstable political environments. If any CMOs on which we will rely fail to manufacture quantities of our product candidates at quality levels necessary to meet regulatory requirements and at a scale sufficient to meet anticipated demand at a cost that allows us to achieve profitability, our business, financial condition and prospects could be materially and adversely affected. In addition, our CMOs are responsible for transporting temperature-controlled materials that can be inadvertently degraded during transport due to several factors, rendering certain batches unsuitable for trial use for failure to meet, among others, our integrity and purity specifications. We and any of our CMOs may also face product seizure or detention or refusal to permit the import or export of products. Our business could be materially adversely affected by business disruptions to our third-party providers that could materially adversely affect our anticipated timelines, potential future revenue and financial condition and increase our costs and expenses. Each of these risks could delay or prevent the completion of our preclinical studies and clinical trials or the approval of any of our product candidates by the FDA, result in higher costs or adversely impact commercialization of our product candidates. See the section titled “Business – Manufacturing” for a more detailed description of our manufacturing plans and assumptions and the factors that may affect the success of our programs.

Risks Related to Employee Matters, Managing Growth and Other Risks Related to Our Business

In order to successfully implement our plans and strategies, we will need to grow the size of our organization and we may experience difficulties in managing this growth.

We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of preclinical and clinical drug development, technical operations, clinical operations, regulatory affairs and, potentially, sales and marketing. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial personnel and 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 working together 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.

We are highly dependent on our key personnel and anticipate hiring new key personnel. If we are not successful in attracting and retaining highly qualified personnel, we may not be able to successfully implement our business strategy.

We are a preclinical stage biotechnology company with a limited operating history, and, as of December 31, 2023, we had 30 employees. We have been and will continue to be highly dependent on the research and

development, clinical and business development expertise of our executive officers, as well as the other principal members of our management, scientific and clinical team. Any of our management team members may terminate their employment with us at any time. We do not maintain "key person" insurance for any of our executives or other employees.

Attracting and retaining qualified personnel will also be critical to our success, including with respect to any strategic transaction that we may pursue. 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, facilitate regulatory approval of and commercialize product candidates. 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.

In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our discovery and nonclinical and clinical development and commercialization strategy. 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. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited.

Our future growth may depend, in part, on our ability to operate in foreign markets, where we would be subject to additional regulatory burdens and other risks and uncertainties.

Our future growth may depend, in part, on our ability to develop and commercialize our product candidates in foreign markets for which we may rely on collaboration with third parties. We are not permitted to market or promote any of our product candidates before we receive regulatory approval from the applicable foreign regulatory authority, and may never receive such regulatory approval for any of our product candidates. To obtain separate regulatory approval in many other countries, we must comply with numerous and varying regulatory requirements of such countries regarding safety and efficacy and governing, among other things, clinical trials and commercial sales, pricing and distribution of our product candidates, and we cannot predict success in these jurisdictions. If we fail to comply with the regulatory requirements in international markets and receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed and our business will be adversely affected. Moreover, even if we obtain approval of our product candidates and ultimately commercialize our product candidates in foreign markets, we would be subject to the risks and uncertainties, including the burden of complying with complex and changing foreign regulatory, tax, accounting and legal requirements and reduced protection of intellectual property rights in some foreign countries.

Our estimates of market opportunity and forecasts of market growth may prove to be inaccurate, and even if the markets in which we compete achieve the forecasted growth, our business may not grow at similar rates, or at all.

Our market opportunity estimates and growth forecasts are subject to significant uncertainty and are based on assumptions and estimates which may not prove to be accurate. Our estimates and forecasts relating to size and expected growth of our target market may prove to be inaccurate. Even if the markets in which we compete meet our size estimates and growth forecasts, our business may not grow at similar rates, or at all. Our growth is subject to many factors, including our success in implementing our business strategy, which is subject to many risks and uncertainties.

Our revenue will be dependent, in part, upon the size of the markets in the territories for which we gain regulatory approval, the accepted price for the product, the ability to obtain coverage and reimbursement and whether we own the commercial rights for that territory. If the number of our addressable patients is not as significant as we estimate, the indication approved by regulatory authorities is narrower than we expect or the treatment population is narrowed by competition, physician choice or treatment guidelines, we may not generate significant revenue from sales of such products, even if approved.

Our employees, independent contractors, consultants, commercial collaborators, principal investigators, CROs, CMOs, suppliers and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk that our employees, independent contractors, consultants, commercial collaborators, principal investigators, CROs, CMOs, suppliers and vendors acting for or on our behalf may engage in misconduct or other improper activities. We have adopted a code of conduct and ethics, but it is not always possible to identify and deter misconduct by these parties and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations.

Our internal information technology systems, or those of any of our CROs, manufacturers, other contractors or consultants, third party service providers, or potential future collaborators, may fail or suffer security or data privacy breaches or other unauthorized or improper access to, use of, or destruction of our proprietary or confidential data, employee data or personal data, which could result in additional costs, loss of revenue, significant liabilities, harm to our brand and material disruption of our operations.

In the ordinary course of our business, we and the third parties upon which we rely collect, receive, store, process, generate, use, transfer, disclose, make accessible, protect, secure, dispose of, transmit, and share (collectively, process) proprietary, confidential, and sensitive data, including personal data, intellectual property, trade secrets, and other sensitive data (collectively, sensitive information).

Despite the implementation of security measures in an effort to protect systems that store our information, given their size and complexity and the increasing amounts of information maintained on our internal information technology systems and those of our third-party CROs, other contractors (including sites performing our clinical trials), third party service providers and supply chain companies, and consultants, these systems are potentially vulnerable to breakdown or other damage or interruption from service interruptions, system malfunction, natural disasters, terrorism, war and telecommunication and electrical failures, as well as security breaches from inadvertent or intentional actions by our employees, contractors, consultants, business partners and/or other third parties, or from cyber-attacks by malicious third parties, which may compromise our system infrastructure or lead to the loss, destruction, alteration or dissemination of, or damage to, our data.

Some actors now engage and are expected to continue to engage in cyber-attacks, including without limitation nation-state actors for geopolitical reasons and in conjunction with military conflicts and defense activities. During times of war and other major conflicts, we, and the third parties upon which we rely, may be vulnerable to a heightened risk of these attacks, including retaliatory cyber-attacks, that could materially disrupt our systems and operations, supply chain, and ability to produce, sell and distribute our goods and services. In particular, severe ransomware attacks are becoming increasingly prevalent and can lead to significant interruptions in our operations, ability to provide our products or services, loss of sensitive data and income, reputational harm, and diversion of funds. Extortion payments may alleviate the negative impact of a ransomware attack, but we may be unwilling or unable to make such payments due to, for example, applicable laws or regulations prohibiting such payments.

To the extent that any disruption or security breach were to result in loss, destruction, unavailability, alteration or dissemination of, or damage to, our data or applications, or for it to be believed or reported that any of these occurred, we could incur liability and reputational damage and the development and commercialization of our product candidates could be delayed. Further, our insurance policies may not be adequate to compensate us for the potential losses arising from any such disruption in, or failure or security breach of, our systems or third-party systems where information important to our business operations or commercial development is stored.

Our fully-remote workforce may create additional risks for our information technology systems and data because our employees work remotely and utilize network connections, computers, and devices working at home, while in transit and in public locations. Additionally, business transactions (such as acquisitions or integrations) could expose us to additional cybersecurity risks and vulnerabilities, as our systems could be negatively affected by vulnerabilities present in acquired or integrated entities' systems and technologies.

While we have implemented security measures designed to protect against security incidents, there can be no assurance that these measures will be effective. We may be unable in the future to detect vulnerabilities

in our information technology systems because such threats and techniques change frequently, are often sophisticated in nature, and may not be detected until after a security incident has occurred. Further, we may experience delays in developing and deploying remedial measures designed to address any such identified vulnerabilities. Applicable data privacy and security obligations may require us to notify relevant stakeholders of security incidents. Such disclosures are costly, and the disclosure or the failure to comply with such requirements could lead to adverse consequences.

We rely on third-party service providers and technologies to operate critical business systems to process sensitive information in a variety of contexts. Our ability to monitor these third parties' information security practices is limited, and these third parties may not have adequate information security measures in place. If our third-party service providers experience a security incident or other interruption, we could experience adverse consequences. While we may be entitled to damages if our third-party service providers fail to satisfy their privacy or security-related obligations to us, any award may be insufficient to cover our damages, or we may be unable to recover such award. In addition, supply-chain attacks have increased in frequency and severity, and we cannot guarantee that third parties' infrastructure in our supply chain or our third-party partners' supply chains have not been compromised.

If we (or a third party upon whom we rely) experience a security incident or are perceived to have experienced a security incident, we may experience adverse consequences, such as government enforcement actions (for example, investigations, fines, penalties, audits, and inspections); additional reporting requirements and/or oversight; restrictions on processing sensitive information (including personal data); litigation (including class claims); indemnification obligations; negative publicity; reputational harm; monetary fund diversions; interruptions in our operations (including availability of data); financial loss; and other similar harms. Security incidents and attendant consequences may cause stakeholders (including investors and potential customers) to stop supporting our platform, deter new customers from products, and negatively impact our ability to grow and operate our business.

Our contracts may not contain limitations of liability, and even where they do, there can be no assurance that limitations of liability in our contracts are sufficient to protect us from liabilities, damages, or claims related to our data privacy and security obligations. We cannot be sure that our insurance coverage will be adequate or sufficient to protect us from or to mitigate liabilities arising out of our privacy and security practices, that such coverage will continue to be available on commercially reasonable terms or at all, or that such coverage will pay future claims.

Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.

Under Section 382 of the Internal Revenue Code of 1986, as amended ("the Code"), if a corporation undergoes an "ownership change," generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards, or NOLs, and other pre-change tax attributes (such as research tax credits) to offset its post-change income or taxes may be limited. Upon certain events since our conversion from a Delaware limited liability company to a Delaware corporation in 2015, it is possible that we may have triggered an "ownership change" limitation. We may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership (some of which are outside of our control). As a result, if we earn net taxable income, our ability to use our pre-change NOLs and other pre-change tax attributes to offset U.S. federal taxable income or taxes may be subject to limitations, which could potentially result in increased future tax liability to us. Our NOLs and other tax attributes arising before our conversion from a Delaware limited liability company to a Delaware corporation in 2015 also may be limited by the Separate Return Limitation Year rule, which could increase our U.S. federal tax liability. In addition, at the state level, there may be periods during which the use of NOLs is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

We are subject to stringent and changing laws, regulations and standards, and contractual obligations relating to privacy, data protection, and data security. The actual or perceived failure to comply with such obligations could lead to government enforcement actions (which could include civil or criminal penalties), fines and sanctions, private litigation and/or adverse publicity and could negatively affect our operating results and business.

We, and third parties who we work with are or may become subject to numerous domestic and foreign laws, regulations, and standards relating to privacy, data protection, and data security, the scope of which is changing, subject to differing applications and interpretations, and may be inconsistent among countries, or conflict with other rules. We are or may become subject to the terms of contractual obligations related to privacy, data protection and data security. Our obligations may also change or expand as our business grows.

The actual or perceived failure by us or third parties related to us to comply with such laws, regulations and obligations could increase our compliance and operational costs, expose us to regulatory scrutiny, actions, fines and penalties, result in reputational harm, lead to a loss of customers, result in litigation and liability, and otherwise cause a material adverse effect on our business, financial condition and results of operations. See the section titled “Business – Government Regulation – Data Privacy and Security” for a more detailed description of the laws that may affect our ability to operate.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

We are 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 may involve the use of hazardous and flammable materials, including chemicals and biological and 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 commercialization efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

We may be subject to adverse legislative or regulatory tax changes that could negatively impact our 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) could adversely affect our stockholders or us. We assess the impact of various tax reform proposals and modifications to existing tax treaties in all jurisdictions where we have operations to determine the potential effect on our business and any assumptions we have made about our future taxable income. We cannot predict whether any specific proposals will be enacted, the terms of any such proposals or what effect, if any, such proposals would have on our business if they were to be enacted. For example, the United States recently enacted the Inflation Reduction Act of 2022, which implements, among other changes, a 1% excise tax on certain stock buybacks. In addition, beginning in 2022, the Tax Cuts and Jobs Act eliminated the previously available option to deduct research and development expenditures and requires taxpayers to amortize them generally over five years for research activities conducted in the United States and over 15 years for research activities conducted outside the United States. The U.S. Congress is considering legislation that would restore the current deductibility of research and development expenditures; however, we have no assurance that the provision will be repealed or otherwise modified. Such changes, among others, may adversely affect our effective tax rate, results of operation and general business condition.

We may acquire businesses or products, or form strategic alliances, in the future, and may not realize the benefits of such acquisitions.

We may acquire additional businesses or products, form strategic alliances, or create joint ventures with third parties that we believe will complement or augment our existing business. If we acquire businesses with promising markets or technologies, we may not be able to realize the benefit of acquiring such businesses if we are unable to successfully integrate them with our existing operations and company culture. We may encounter numerous difficulties in developing, manufacturing and marketing any new product candidates or products resulting from a strategic alliance or acquisition that delay or prevent us from realizing their expected benefits or enhancing our business. There is no assurance that, following any such acquisition, we will achieve the synergies expected in order to justify the transaction, which could result in a material adverse effect on our business and prospects.

We maintain our cash at financial institutions, often in balances that exceed federally-insured limits. The failure of financial institutions could adversely affect our ability to pay our operational expenses or make other payments.

Our cash held in non-interest-bearing and interest-bearing accounts exceeds the Federal Deposit Insurance Corporation ("FDIC") insurance limits. If such banking institutions were to fail, we could lose all or a portion of those amounts held in excess of such insurance limitations. For example, the FDIC took control of Silicon Valley Bank on March 10, 2023. The Federal Reserve subsequently announced that account holders

would be made whole. However, the FDIC may not make all account holders whole in the event of future bank failures. In addition, even if account holders are ultimately made whole with respect to a future bank failure, account holders' access to their accounts and assets held in their accounts may be substantially delayed. Any material loss that we may experience in the future or inability for a material time period to access our cash and cash equivalents could have an adverse effect on our ability to pay our operational expenses or make other payments, which could adversely affect our business.

Risks Related to Our Common Stock

Pursuant to the terms of the December 2023 SPA, we are required to recommend that our stockholders approve the conversion of all outstanding shares of our Series B Preferred Stock into shares of our common stock. We cannot guarantee that our stockholders will approve this matter, and if they fail to do so, we may be required to settle such shares in cash and our operations may be materially harmed.

Under the terms of the December 2023 SPA, we agreed to use best efforts to obtain the requisite approval for the conversion of all outstanding shares of Series B Preferred Stock issued in the December 2023 PIPE into shares of our common stock, as required by the Nasdaq listing rules, at our 2024 annual meeting of stockholders and, if such approval is not obtained at that meeting, to seek to obtain such approval at a stockholders meeting to be held at least every 90 days thereafter until such approval is obtained, which would be time consuming and costly. Additionally, if our stockholders do not timely approve the conversion of our Series B Preferred Stock, then the holders of our Series B Preferred Stock may be entitled to require us to settle their shares of Series B Preferred Stock for cash at a price per share equal to the fair value of the Series B Preferred Stock at such time, as described in our Series B Certificate of Designation relating to the Series B Preferred Stock. If we are forced to settle a significant amount of the Series B Preferred Stock, it could materially affect our results of operations.

Anti-takeover provisions in our charter documents and under Delaware law and the terms of some of our contracts could make an acquisition of us more difficult and may prevent attempts by our stockholders to replace or remove our management.

Provisions in our Certificate of Incorporation and Bylaws may delay or prevent an acquisition or a change in management. These provisions include a prohibition on actions by written consent of our stockholders and the ability of our board of directors to issue Preferred Stock without stockholder approval. In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the DGCL, which prohibits stockholders owning in excess of 15% of our outstanding voting stock from merging or combining with us. Although we believe these provisions collectively will provide for an opportunity to receive higher bids by requiring potential acquirers to negotiate with our board of directors, they would apply even if the offer may be considered beneficial by some stockholders. In addition, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove then current management by making it more difficult for stockholders to replace members of the board of directors, which is responsible for appointing the members of management.

In addition, the Series A Certificate of Designation relating to our Series A Preferred Stock may delay or prevent a change in control of our company. At any time while at least 30% of the originally issued Series A Preferred Stock remains issued and outstanding, we may not consummate a Fundamental Transaction (as defined in the Series Certificate of Designation) or any merger or consolidation of the Company with or into another entity or any stock sale to, or other business combination in which our stockholders immediately before such transaction do not hold at least a majority of our capital stock immediately after such transaction, without the affirmative vote of the holders of a majority of the then outstanding shares of the Series A Preferred Stock. This provision of the Series A Certificate of Designation may make it more difficult for us to enter into any of the aforementioned transactions.

Our Certificate of Incorporation and Bylaws provide that the Court of Chancery of the State of Delaware is the exclusive forum certain types of actions and proceedings that may be initiated by our stockholders, and our Bylaws designate the federal courts of the United States as the exclusive forum for actions arising under the Securities Act, each of which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers, employees or agents.

Our Certificate of Incorporation and Bylaws provide that, unless we consent in writing to an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for any derivative action or proceeding brought on our behalf, any action asserting a claim of breach of a fiduciary duty owed by

any of our directors, officers, employees or agents to us or our stockholders, any action asserting a claim arising pursuant to any provision of the DGCL, our Certificate of Incorporation or our Bylaws or any action asserting a claim that is governed by the internal affairs doctrine, in each case subject to the Court of Chancery having personal jurisdiction over the indispensable parties named as defendants therein and the claim not being one which is vested in the exclusive jurisdiction of a court or forum other than the Court of Chancery or for which the Court of Chancery does not have subject matter jurisdiction. Any person purchasing or otherwise acquiring any interest in any shares of our capital stock shall be deemed to have notice of and to have consented to this provision of our Certificate of Incorporation and Bylaws.

Our Bylaws provide that the federal district courts of the United States of America will, to the fullest extent permitted by law, be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act (a “Federal Forum Provision”). Our decision to adopt a Federal Forum Provision followed a decision by the Supreme Court of the State of Delaware holding that such provisions are facially valid under Delaware law. While there can be no assurance that federal or state courts will follow the holding of the Delaware Supreme Court or determine that the Federal Forum Provision should be enforced in a particular case, application of the Federal Forum Provision means that suits brought by our stockholders to enforce any duty or liability created by the Securities Act must be brought in federal court and cannot be brought in state court. In addition, investors cannot waive compliance with the federal securities laws and the rules and regulations thereunder.

These choice of forum provisions will not apply to claims brought to enforce a duty or liability created by the Exchange Act. These choice of forum provisions may limit our stockholders’ ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers, employees or agents, which may discourage such lawsuits against us and our directors, officers, employees and agents even though an action, if successful, might benefit our stockholders. Stockholders who do bring a claim in the specified courts could face additional litigation costs in pursuing any such claim. The specified courts may also reach different judgments or results than would other courts, including courts where a stockholder considering an action may be located or would otherwise choose to bring the action, and such judgments or results may be more favorable to us than to our stockholders. Alternatively, if a court were to find these provisions of our governance documents inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could have a material adverse effect on our business, financial condition or results of operations.

We do not anticipate that we will pay any cash dividends in the foreseeable future.

The current expectation is that we will retain our future earnings, if any, to fund the development and growth of our business. As a result, capital appreciation, if any, of our common stock will be your sole source of gain, if any, for the foreseeable future.

Future sales of shares by existing stockholders could cause our stock price to decline.

On December 7, 2023, we entered into a registration rights agreement (the “December 2023 RRA”) with the December 2023 Investors. Pursuant to the December 2023 RRA, we agreed to file a resale registration statement to register the Registrable Securities (as defined in the December 2023 RRA) (the "Registration Statement"). The registration statement was filed on December 22, 2023 in order to satisfy our obligations under the December 2023 RRA. We have agreed to use our commercially reasonable efforts to cause the Registration Statement to be declared effective by the SEC as soon as practicable. If, following receipt of stockholder approval of the conversion of all issued and outstanding Series B Preferred Stock into shares of common stock in accordance with the Nasdaq Stock Market Rules (the “Series B Conversion Proposal"), the Registration Statement is not declared effective prior to, subject to certain limited exceptions pursuant to the December 2023 RRA, the 90th calendar day following the closing date of the December 2023 PIPE (or, in the event the SEC reviews and has written comments to the Registration Statement, the 120th calendar day following such closing date), among other events (each event, a “Registration Failure”), then we will be required to make pro rata payments to each Investor of the then outstanding Registrable Securities in an amount equal to one percent of the aggregate amount invested by such December 2023 Investor for the Registrable Securities then held by such December 2023 Investor for the initial day of a Registration Failure and for each 30 day period thereafter until the Registration Failure is cured. If the Registration Statement is declared effective, the shares subject to the Registration Statement will no longer constitute restricted securities and may be sold freely in the public markets, subject to lapse on any related contractual restrictions related thereto of any

December 2023 Investor and, for shares of common stock issuable upon the conversion of Series B Preferred Stock, the approval of our stockholders of such conversion.

If our stockholders sell, or indicate an intention to sell, substantial amounts of our common stock in the public market after legal restrictions on resale lapse, the trading price of our common stock could decline. In addition, shares of our common stock that are subject to our outstanding options will become eligible for sale in the public market to the extent permitted by the provisions of various vesting agreements and Rules 144 and 701 under the Securities Act.

Future sales and issuances of equity and debt could result in additional dilution to our stockholders.

We expect that we will need significant additional capital to fund our current and future operations, including to complete potential clinical trials for our product candidates. To raise capital, we may sell common stock, convertible securities, or other equity securities in one or more transactions at prices and in a manner we determine from time to time. As a result, our stockholders may experience additional dilution, which could cause our stock price to fall.

Pursuant to our equity incentive plans, we may grant equity awards and issue additional shares of our common stock to our employees, directors and consultants, and the number of shares of our common stock reserved for future issuance under certain of these plans will be subject to automatic annual increases in accordance with the terms of the plans. To the extent that new options are granted and exercised, or we issue additional shares of common stock in the future, our stockholders may experience additional dilution, which could cause our stock price to fall.

Our principal stockholders own a significant percentage of our stock and are able to exert significant control over matters subject to stockholder approval.

Our directors, officers, 5% stockholders, and their affiliates currently beneficially own a substantial portion of our outstanding voting stock. Therefore, these stockholders have the ability and may continue to have the ability to influence us through this ownership position. These stockholders may be able to determine some or all matters requiring stockholder approval. For example, these stockholders, acting together, may be able to control elections of directors, amendments of organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may believe are in your best interest as one of our stockholders.

General Risk Factors

The market price of our common stock has historically been volatile, and the market price of our common stock may decline in the future.

The market price of our common stock has been, and may continue to be, subject to significant fluctuations. Market prices for securities of early-stage pharmaceutical, biotechnology, and other life sciences companies have historically been particularly volatile. Some of the factors that may cause the market price of our common stock to fluctuate include:

- our ability to obtain regulatory approvals for our product candidates, and delays or failures to obtain such approvals;
- failure of any of our product candidates, if approved, to achieve commercial success;
- failure to maintain our existing third-party license and supply agreements;
- changes in laws or regulations applicable to our product candidates;
- any inability to obtain adequate supply of our product candidates or the inability to do so at acceptable prices;
- adverse regulatory authority decisions;
- introduction of new products, services, or technologies by our competitors;
- failure to meet or exceed financial and development projections we may provide to the public and the investment community;

- the perception of the pharmaceutical industry by the public, legislatures, regulators, and the investment community;
- announcements of significant acquisitions, strategic collaborations, joint ventures, or capital commitments by us or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters, and our ability to obtain patent protection for our technologies;
- additions or departures of key personnel;
- significant lawsuits, including patent or stockholder litigation;
- if securities or industry analysts do not publish research or reports about our business, or if they issue an adverse or misleading opinion regarding our business and stock;
- changes in the market valuations of similar companies;
- general market or macroeconomic conditions, including global inflationary pressures, rising interest rates, general economic slowdown or a recession, changes in monetary policy, instability in financial institutions and the prospect of a shutdown of the U.S. federal government;
- geopolitical instability, including the ongoing military conflict in Ukraine, conflict in Israel and surrounding areas, and geopolitical tensions in China;
- sales of our common stock by us or our stockholders in the future;
- trading volume of our common stock;
- announcements by commercial partners or competitors of new commercial products, clinical progress or the lack thereof, significant contracts, commercial relationships, or capital commitments;
- the introduction of technological innovations or new therapies that compete with our potential products;
- changes in the structure of health care payment systems; and
- period-to-period fluctuations in our financial results.

Moreover, the capital markets in general have experienced substantial volatility that has often been unrelated to the operating performance of individual companies. These broad market fluctuations may also adversely affect the trading price of our common stock.

In the past, following periods of volatility in the market price of a company's securities, stockholders have often instituted class action securities litigation against those companies. Such litigation, if instituted, could result in substantial costs and diversion of management attention and resources, which could significantly harm our profitability and reputation.

We incur costs and demands upon management as a result of complying with the laws and regulations regulating public companies.

We incur significant legal, accounting, and other expenses associated with public company reporting requirements. We also incur costs associated with corporate governance requirements, including requirements under the Sarbanes-Oxley Act, as well as rules implemented by the SEC and Nasdaq. These rules and regulations increase our legal and financial compliance costs and make some activities more time-consuming and costly. These rules and regulations may also make it difficult and expensive for us to obtain directors' and officers' liability insurance. As a result, it may be more difficult for us to attract and retain qualified individuals to serve on our board of directors or as our executive officers, which may adversely affect investor confidence and could cause our business or stock price to suffer.

If equity research analysts do not publish research or reports, or publish unfavorable research or reports, about us, our business, or our market, our stock price and trading volume could decline.

The trading market for our common stock is influenced by the research and reports that equity research analysts publish about us and our business. Equity research analysts may elect not to provide research coverage of our common stock and such lack of research coverage may adversely affect the market price of our common stock. In the event we do have equity research analyst coverage, we will not have any control over the analysts or the content and opinions included in their reports. The price of our common stock could decline if one or more equity research analysts downgrade our stock or issue other unfavorable commentary or research. If one or more equity research analysts ceases coverage of us or fails to publish reports on us regularly, demand for our common stock could decrease, which in turn could cause our stock price or trading volume to decline.

If we fail to maintain proper and effective internal controls, our ability to produce accurate financial statements on a timely basis could be impaired, investors may lose confidence in the accuracy and completeness of our financial reports and the market price of our common stock may be negatively affected.

We are subject to the reporting requirements of the Exchange Act, the Sarbanes-Oxley Act, and the rules and regulations of Nasdaq. The Sarbanes-Oxley Act requires, among other things, that we maintain effective disclosure controls and procedures and internal control over financial reporting. We must perform system and process evaluation and testing of our internal control over financial reporting to allow management to report on the effectiveness of our internal controls over financial reporting in our annual report filing for that year, as required by Section 404 of the Sarbanes-Oxley Act. This requires that we incur substantial professional fees and internal costs to expand our accounting and finance functions and that we expend significant management efforts. We may experience difficulty in meeting these reporting requirements in a timely manner for each period.

We may or any subsequent testing by our independent registered public accounting firm may discover weaknesses in our system of internal financial and accounting controls and procedures that could result in a material misstatement of our financial statements. Our internal control over financial reporting will not prevent or detect all errors and all fraud. A control system, no matter how well designed and operated, can provide only reasonable, not absolute, assurance that the control system's objectives will be met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that misstatements due to error or fraud will not occur or that all control issues and instances of fraud will be detected.

If we are not able to comply with the requirements of Section 404 of the Sarbanes-Oxley Act, or if we are unable to maintain proper and effective internal controls, it could result in a material misstatement of our financial statements that would not be prevented or detected on a timely basis, which could require a restatement, cause us to be subject to sanctions or investigations by Nasdaq, the SEC, or other regulatory authorities, cause investors to lose confidence in our financial information, or cause our stock price to decline.

As a public company, we incur significant legal, accounting, insurance, and other expenses, and our management and other personnel have and will need to continue to devote a substantial amount of time to compliance initiatives resulting from operating as a public company.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 1C. CYBERSECURITY

In the ordinary course of our business, we collect, use, store, and transmit digitally confidential, sensitive, proprietary, personal, and health-related information. The secure maintenance of this information and our information technology systems is important to our operations and business strategy. To this end, we have implemented processes using the cybersecurity risk framework published by the National Institute of Standards and Technology ("NIST") designed to assess, identify, and manage risks from potential unauthorized occurrences on or through our information technology systems that may result in adverse effects on the confidentiality, integrity, and availability of these systems and the data residing therein. These processes are managed and monitored by a dedicated information technology team, which is led by our Senior Vice President, Operations and our Vice President, Information Technology ("IT"), and include mechanisms, controls, technologies, systems, and other processes designed to prevent or mitigate data loss, theft, misuse, or other security incidents or vulnerabilities affecting the data and maintain a stable information technology environment. Specific measures include regular penetration and vulnerability testing, data recovery testing, security audits, and ongoing risk assessments. We conduct due diligence on and audits of key technology vendors, contract research organizations (CROs), and other third-party contractors and suppliers. Additionally, we conduct periodic employee training that covers cyber and information security, among other topics. We also regularly consult with outside advisors and experts. Their assistance helps us assess, identify, and manage cybersecurity risks, anticipate future threats and trends, and understand their potential impact on our risk environment.

Our Vice President, Information Technology, who reports directly to our Senior Vice President, Operations, has over 25 years of experience managing information technology and cybersecurity matters and is certified as Certified Information Systems Security Professional. Together with our Senior Vice President, Operations and the other members of our senior leadership team, our Vice President, Information Technology is responsible for assessing and managing cybersecurity risks. We consider cybersecurity, along with other significant risks that we face, within our overall enterprise risk management framework. In the last fiscal year, we have not identified risks from known cybersecurity threats, including as a result of any prior cybersecurity incidents, that have materially affected us, but we face certain ongoing cybersecurity risks threats that, if realized, are reasonably likely to materially affect us. Additional information on cybersecurity risks we face is discussed in Part I, Item 1A, “Risk Factors,” under the heading “Our internal information technology systems, or those of any of our CROs, manufacturers, other contractors or consultants, third party service providers, or potential future collaborators, may fail or suffer security or data privacy breaches or other unauthorized or improper access to, use of, or destruction of our proprietary or confidential data, employee data or personal data, which could result in additional costs, loss of revenue, significant liabilities, harm to our brand and material disruption of our operations.”

The Board of Directors, as a whole and at the committee level, has oversight for the most significant risks facing us and for our processes to identify, prioritize, assess, manage, and mitigate those risks. The Audit Committee, which is comprised solely of independent directors, has been designated by our Board to oversee cybersecurity risks. The Audit Committee receives regular updates on cybersecurity and information technology matters and related risk exposures from our Vice President, Information Technology, as well as other members of the senior leadership team. The Board also receives updates from management and the Audit Committee on cybersecurity risks on at least an annual basis.

ITEM 2. PROPERTIES

We do not maintain physical corporate offices. Our employees work remotely. We believe these arrangements support our current needs. We maintain a mailing address at 221 Crescent St., Building 23, Suite 105, Waltham, MA 02453. As we expand, we believe that suitable additional alternative spaces will be available in the future on commercially reasonable terms, if required.

ITEM 3. LEGAL PROCEEDINGS

From time to time, we may become involved in legal proceedings relating to claims arising from the ordinary course of business. Our management believes that there are currently no claims or actions pending against us, the ultimate disposition of which could have a material adverse effect on our results of operations, financial condition or cash flows.

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 and Holders

Our common stock is traded on The Nasdaq Stock Market LLC under the symbol "SYRE."

As of February 21, 2024, there were approximately 65 stockholders of record of our common stock based on information provided by our transfer agent. The actual number of stockholders is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

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 to support our operations and finance the growth and development of our business. We do not intend to pay cash dividends on our common stock for the foreseeable future.

Recent Sales of Unregistered Securities

None.

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

ITEM 6. [RESERVED]

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion and analysis of our financial condition and results of operations together with our financial statements and related notes appearing in this Annual Report. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report, 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, 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. As used in this report, unless the context suggests otherwise, "we", "us", "our", "the Company," "Aeglea BioTherapeutics, Inc." or "Spyre" refers to Spyre Therapeutics, Inc. and its consolidated subsidiaries, including Spyre Therapeutics, LLC, taken as a whole.

Acquisition of Pre-Merger Spyre

On June 22, 2023, we acquired Pre-Merger Spyre pursuant to the Acquisition Agreement. Pre-Merger Spyre was a pre-clinical stage biotechnology company that was incorporated on April 28, 2023 under the direction of Peter Harwin, a Managing Member of Fairmount, for the purpose of holding rights to certain intellectual property being developed by Paragon. Fairmount is a founder of Paragon.

Through the Asset Acquisition, we received the Option to license the in-process research and development ("IPR&D") rights related to four research programs. On July 12, 2023, we exercised the Option with respect to one of these research programs to exclusively license intellectual property rights related to such research program directed to antibodies that selectively bind to α4β7 integrin and methods of using these antibodies, including methods of treating IBD using SPY001. If this research program is pursued non-provisionally and matures into issued patents, we would expect those patents to expire no earlier than 2044, subject to any disclaimers or extensions. On December 14, 2023, we exercised the Option under the Paragon Agreement to be granted an exclusive license to all of Paragon's rights, title and interest in and to intellectual property rights, including inventions, patents, sequence information and results, under SPY002, our TL1A program, to develop and commercialize antibodies and products worldwide in all therapeutics disorders. The license agreements pertaining to such research programs are currently being finalized on previously agreed terms. Furthermore, as of the date of this Annual Report, the Option remains unexercised with respect to the IPR&D rights related to the two remaining research programs under the Paragon Agreement.

Overview

Following the Asset Acquisition and the entry into the Immedica APA, we have significantly reshaped the business into a preclinical stage biotechnology company focused on developing next generation therapeutics for patients living with IBD, including UC and CD. Through the Paragon Agreement, our portfolio of novel and proprietary monoclonal antibody product candidates has the potential to address unmet needs in IBD care by improving efficacy, safety, and/or dosing convenience relative to products currently available or product candidates in development. We have engineered our product candidates with the aim to bind potently and selectively to their target epitopes and to exhibit extended pharmacokinetic half-lives through modifications in the Fc domain, which modifications are designed to increase affinity to human FcRn and increase antibody recycling. We anticipate that half-life extension will enable less frequent administration as compared to marketed or development-stage mAbs that do not incorporate half-life extension modifications. In addition to the development of our product candidates as potential monotherapies, we plan to investigate combinations of our proprietary antibodies in preclinical and clinical studies in order to evaluate whether combination therapy (co-administration or co-formulation of multiple monoclonal antibodies) can lead to greater efficacy, as compared to monotherapies in IBD. We also intend to examine patient selection strategies via complementary diagnostics utilized in our clinical studies to evaluate whether patients may be matched to the optimal therapy based on genetic background and/or other biomarker signatures. We intend to deliver our product candidates through convenient, infrequently self-administered, subcutaneous injections, although the specific delivery mechanism or technology has not been selected given our early stage.

Business and Macroeconomic Conditions

The extent of the impact of macroeconomic events and conditions, including inflation, increasing interest rates, increasing financial market volatility and uncertainty, the impact of geopolitical instabilities, including the ongoing military conflict in Ukraine, conflict in Israel and surrounding areas, and geopolitical tensions in China, and its potential supply chain impact, and public health pandemics, including the COVID-19 pandemic and its variants, on our operational and financial performance will continue to depend on certain developments, including the impact on our clinical studies, employee or industry events, and effect on our suppliers and manufacturers, all of which are uncertain and cannot be predicted. Adverse effects of these large macroeconomic conditions have been prevalent in many of the areas where we, our clinical research organizations ("CROs"), suppliers or third-party business partners conduct business and as a result, we may experience disruptions in our operations. We have experienced and may in the future experience such disruption or delays due to these factors as well as delays due to labor shortages and supply chain disruptions in distribution of clinical trial materials, study monitoring and data analysis that could materially adversely impact our business, results of operations and overall financial performance in future periods. As of the filing date of this Annual Report, the extent to which these macroeconomic events and conditions may impact our financial condition, results of operations or guidance is uncertain. The effect of these macroeconomic events and conditions may not be fully reflected in our results of operations and overall financial performance until future periods. See Part I, Item 1A “Risk Factors” for further discussion of the possible impact of these macroeconomic conditions on our business.

Components of Operating Results

Revenue

We have recognized license and development revenue from the Immedica Agreement (as defined below) related to our legacy product candidate pegzilarginase. On July 27, 2023, we announced that we entered into an agreement to sell the global rights to pegzilarginase to Immedica. The sale of pegzilarginase to Immedica superseded and terminated the Immedica Agreement.

We have not generated any revenue from commercial product sales. Our ability to generate product revenues in the future will depend on the successful development, regulatory approval, and commercialization of our product candidates.

Licensing and Sale of Pegzilarginase

In March 2021, we licensed to Immedica the rights to the commercialization of pegzilarginase in the European Economic Area, United Kingdom, Switzerland, Andorra, Monaco, San Marino, Vatican City, Turkey, Saudi Arabia, United Arab Emirates, Qatar, Kuwait, Bahrain, and Oman (the "Immedica Agreement"). The Immedica Agreement included a non-refundable upfront payment of $21.5 million from Immedica and up to $3.0 million of payments for development services provided to Immedica. Under the terms of the Immedica Agreement, we were eligible to receive additional regulatory and commercial milestone payments and were entitled to receive royalties in the mid-20% range on net sales of the product in countries included in the Immedica Agreement.

For the twelve months ended December 31, 2023 and 2022, we recognized revenue of $0.9 million and $2.3 million, respectively, under the Immedica Agreement. The total revenue generated for the twelve months ended December 31, 2023 was attributable to the PEACE Phase 3 trial and PIP trials, drug supply, and royalties from an early access program in France. For the twelve months ended December 31, 2022, the revenue recognized was related to the PEACE Phase 3 trial and BLA package performance.

On July 27, 2023, we announced that we entered into an agreement to sell the global rights to pegzilarginase to Immedica for $15.0 million in upfront cash proceeds and up to $100.0 million in contingent milestone payments. The sale of pegzilarginase to Immedica superseded and terminated the Immedica Agreement. On July 27, 2023, the carrying value of the asset was zero as it was internally developed. Accordingly, we recognized a $16.4 million gain within Gain on sale of in-process research and development,

which is comprised of $15.0 million in upfront cash proceeds and the reimbursement of $1.8 million in pre-paid manufacturing costs that was contingent upon a favorable opinion being received by the CHMP, net of transaction costs and the derecognition of pegzilarginase related nonfinancial assets and liabilities totaling $0.4 million.

The milestone payments are contingent on formal reimbursement decisions by national authorities in key European markets and pegzilarginase approval by the FDA, among other events. The upfront payment and contingent milestone payments if paid, net of expenses and adjustments, will be distributed to holders of our CVRs (as defined below) pursuant to the contingent value rights agreement (the "CVR Agreement") we entered into with Equiniti Trust Company LLC (f/k/a American Stock Transfer & Trust Company LLC) as rights agent in connection with the Asset Acquisition.

Research and development expenses

Research and development expenses consist primarily of costs incurred for the discovery and development of our product candidates, historically including pegtarviliase and pegzilarginase, and now focused on our portfolio of IBD product candidates. We contract with external providers for nonclinical studies and clinical trials. Our research and development expenses include:

- costs from acquiring clinical trial materials and services performed for contracted services with contract manufacturing organizations, or CMOs;
- fees paid to clinical trial sites, CROs, CMOs, nonclinical research companies, and academic institutions;
- direct and pass through costs associated with research conducted under the Paragon Agreement; and
- employee and consultant-related expenses incurred, which include salaries, benefits, travel, and stock-based compensation.

Research and development costs are expensed as incurred. Advance payments for goods or services to be rendered in the future for use in research and development activities are deferred and capitalized. The capitalized amounts are expensed as the related goods are delivered or the services are performed.

Research and development expenses have historically represented the largest component of our total operating expenses.

Our expenditures on current and future nonclinical and clinical development programs are subject to numerous uncertainties in timing and cost to completion. The duration, costs, and timing of nonclinical activities, clinical trials, and development of our product candidates will depend on a variety of factors, including:

- the scope, rate of progress, and expenses of our ongoing research activities as well as any additional nonclinical activities, clinical trials, and other research and development activities;
- future clinical trial results;
- uncertainties in clinical trial enrollment rates or drop-out or discontinuation rates of patients;
- changes in the competitive drug development environment;
- potential safety monitoring or other studies requested by regulatory agencies;
- significant and changing government regulation;
- the timing and receipt of regulatory approvals, if any; and
- macroeconomic events and conditions, including inflation, increasing interest rates, increasing financial market volatility and uncertainty, the impact of geopolitical instabilities, including ongoing military conflict in Ukraine, conflict in Israel and surrounding areas, and geopolitical tensions in China, and its potential supply chain impact, and public health pandemics, such as the COVID-19 pandemic.

The process of conducting the necessary clinical research to obtain FDA and other regulatory approval is costly and time consuming and the successful development of our product candidates is highly uncertain. The risks and uncertainties associated with our research and development projects are discussed more fully in Part I, Item 1A of this Annual Report titled “Risk Factors.” As a result of these risks and uncertainties, we are unable to determine with any degree of certainty the duration and completion costs of our research and development projects, or if, when, or to what extent we will generate revenues from the commercialization and sale of any of our product candidates that obtain regulatory approval. We may never succeed in achieving regulatory approval for any of our product candidates.

General and administrative expenses

General and administrative expenses consist primarily of salaries and other related costs, including stock-based compensation, for personnel in executive, finance, accounting, legal, corporate development, information technology, and human resources functions. Other significant costs include legal fees relating to corporate matters and fees for insurance, accounting, consulting, facilities, and recruiting services.

We expect that our general and administrative expenses will increase in the future to support our continued research and development activities. These increases will likely include higher costs related to the hiring of additional personnel and fees to outside consultants, lawyers and accountants, among other expenses. Additionally, we have incurred and expect to continue to incur increased costs associated with being a public company, including expenses related to services associated with maintaining compliance with Nasdaq listing rules and SEC requirements, insurance, and investor relations costs.

Restructuring

On April 12, 2023, based on the review of the inconclusive interim results from our Phase 1/2 clinical trial of pegtarviliase for the treatment of classical homocystinuria and other business considerations, we announced that we had initiated a process to explore strategic alternatives to maximize stockholder value and engaged an independent exclusive financial advisor to support this process. As a result, we implemented a restructuring plan that resulted in an approximate 83% reduction of our existing headcount by June 30, 2023.

All charges related to the restructuring activities were recognized during the twelve months ended December 31, 2023. No further restructuring charges will be incurred under the restructuring plan.

Severance and Stock Compensation

We recognized restructuring expenses consisting of cash severance payments and other employee-related costs of $6.4 million during the twelve months ended December 31, 2023. Cash payments for employee related restructuring charges of $5.3 million were paid as of December 31, 2023. In addition, we recognized $1.0 million in non-cash stock-based compensation expense related to the accelerated vesting of stock-based awards for certain employees. We recorded these restructuring charges based on each employee’s role to the respective research and development and general and administrative operating expense categories on its consolidated statements of operations and comprehensive loss.

Sale of Assets

During the second quarter of 2023, we sold various lab equipment, consumables, and furniture and fixtures for total consideration of $0.5 million. After recording the disposal of all our property and equipment net of proceeds, we recorded a $0.7 million and $0.2 million loss on disposal of long lived assets which is included in Research and development and General and administrative expenses, respectively.

Lease Right-of-use Asset and Leasehold Improvement Impairment

Effective June 30, 2023, we abandoned our leased office space in Austin, Texas. As a result, we recognized an impairment loss of $0.9 million related to the operating lease right-of-use asset and $1.7 million related to leasehold improvements. On August 7, 2023, we terminated our building lease in Austin, Texas. The negotiated termination agreement obligated us to pay the lessor a $2.0 million termination fee in exchange for releasing us of all further obligations under the lease. All charges related to the restructuring activities were

recognized during the second quarter of 2023. No further restructuring charges will be incurred under the restructuring plan.

Interest income

Interest income consists of interest earned on our cash, cash equivalents, marketable securities, and restricted cash.

Income taxes

We serve as a holding company for our eleven wholly owned subsidiary corporations in the United States, United Kingdom, and European Union. We file a consolidated U.S. corporate federal income tax return with our nine United States subsidiaries. Additionally, we operate in the United Kingdom. Our Irish entity is dormant. Our income tax returns are subject to audit and adjustment by the taxing authorities. We use the asset and liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are recognized for the expected future tax consequences of temporary differences between the financial statements and the tax bases of assets and liabilities. A valuation allowance is established against the deferred tax assets to reduce their carrying value to an amount that is more likely than not to be realized. The deferred tax assets and liabilities are classified as noncurrent along with the related valuation allowance. Due to our lack of earnings history, the net deferred tax assets have been fully offset by a valuation allowance.

We recognize benefits of uncertain tax positions if it is more likely than not that such positions will be sustained upon examination based solely on the technical merits, as the largest amount of benefits that is more likely than not to be realized upon the ultimate settlement. Our policy is to recognize interest and penalties related to the unrecognized tax benefits as a component of income tax expense.

Critical Accounting Policies and Estimates

Our consolidated financial statements are prepared in accordance with generally accepted accounting principles in the United States ("U.S. GAAP"). The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets, liabilities, revenue, costs and expenses, and related disclosures. These estimates form the basis for judgments we make about the carrying values of our assets, liabilities and equity and the amount of revenues and expenses, which are not readily apparent from other sources. We base our estimates on historical experience and on various other assumptions that we believe are reasonable under the circumstances. On an ongoing basis, we evaluate our estimates and assumptions. Our actual results may differ materially from these estimates under different assumptions or conditions.

Our critical accounting policies are those policies which require the most significant judgments and estimates in the preparation of our consolidated financial statements. The most significant estimates and assumptions that management considers in the preparation of our financial statements relate to accrued research and development costs; the valuation of consideration transferred in acquiring in-process research and development ("IPR&D"); the discount rate, probabilities of success, and timing of estimated cash flows in the valuation of the CVR liability; inputs used in the Black-Scholes model for stock-based compensation expense; estimated future cash flows used in calculating the impairment of right-of-use lease assets; and estimated cost to complete performance obligations related to revenue recognition. The consideration transferred in acquiring IPR&D in connection with the acquisition of Pre-Merger Spyre was comprised of our Common Stock and shares of Series A Preferred Stock. To determine the fair value of the equity transferred, we considered the per share value of our PIPE financing that closed in June 2023 (the "June 2023 PIPE"), which was a financing involving a group of accredited investors.

We define our critical accounting policies as those accounting principles generally accepted in the United States that require us to make subjective estimates and judgments about matters that are uncertain and are likely to have a material impact on our financial condition and results of operations, as well as the specific manner in which we apply those principles. Our significant accounting policies are more fully described in Note 2 to our consolidated financial statements included elsewhere in this Annual Report.

Revenue recognition

We enter into license agreements related to our technologies that we have determined are within the scope of Accounting Standards Codification 606. Based on the terms and conditions of our agreements, we identify the goods and services that we promise to transfer to the customer, which may consist of the licensing of technologies, the performance of research and development activities, and/or the supply of products related to our technologies. Based on the nature of the goods and services provided and the customer's intended benefit of the arrangement, we evaluate which of the promised goods and services are distinct and, therefore, represent a performance obligation, which may require us to combine certain promised goods and services that are determined to not be distinct from one another. We also evaluate whether an agreement provides the customer an option to purchase future goods or services at a discounted price, or a material right, which would also represent a performance obligation.

In exchange for the performance obligations, we estimate the amount of consideration promised by the customer, or transaction price, which may include both fixed and variable consideration. Variable consideration, which may consist of various milestone payments based upon the achievement of certain events or conditions, sales-based royalties, or payments contingent on the performance of research and development services, are included in the transaction price only if we expect to receive such consideration and determine it is likely that the inclusion of the variable consideration will not result in a significant reversal in the cumulative amount of revenue recognized under the arrangement. Sales-based royalty and milestone payments that we determine are predominantly related to the license of our intellectual property are excluded from the transaction price we expect to receive until the underlying sales occur.

We allocate the estimated transaction price to the identified performance obligations based on the relative estimated stand-alone selling price ("SSP") of each performance. SSP is based on the observable price of our goods and services, or when SSP is not directly observable, we estimate SSP based on factors such as forecasted revenues or costs, development timelines, discount rates, probabilities of technical and regulatory success, and considerations such as market conditions and entity-specific factors. We recognize revenue allocated to each performance obligation either at a point-in-time or over time in a manner that depicts the transfer of control of the promised goods and services to the customer. For performance obligations that are recognized over time, we estimate the measure of progress associated with the satisfaction of the performance obligation based on an input or output method, which may be based on factors such as costs incurred, labor hours expended, time elapsed, among other measures based on the nature of the performance obligation. The estimates made on an input or output method are subject to change and may result in material changes to revenue that could materially affect our results of operations. Please refer to Note 12, Strategic License Agreements, to the consolidated financial statements included elsewhere in this Annual Report.

Accrued research and development costs

We record the costs associated with research nonclinical studies, clinical trials, and manufacturing as incurred. These costs are a significant component of our research and development expenses, with a substantial portion of our on-going research and development activities conducted by third-party service providers, including CROs, CMOs, and our related-party Paragon.

We accrue for expenses resulting from obligations under the Paragon Agreement and agreements with CROs, CMOs, and other outside service providers for which payment flows do not match the periods over which materials or services are provided to us. We record accruals based on estimates of services received and efforts expended pursuant to agreements established with Paragon, CROs, CMOs, and other outside service providers. These estimates are typically based on contracted amounts applied to the proportion of work performed and determined through analysis with internal personnel and external service providers as to the progress or stage of completion of the services. We make significant judgments and estimates in determining the accrual balance in each reporting period. In the event advance payments are made to Paragon, a CRO, a CMO, or an outside service provider, the payments will be recorded as a prepaid asset which will be amortized as the contracted services are performed. As actual costs become known, we adjust our accruals. Inputs, such as the services performed, the number of patients enrolled, or the study duration, may vary from our estimates, resulting in adjustments to research and development expense in future periods. Changes in these estimates that result in material changes to our accruals could materially affect our results of operations. However, there have been no material changes in estimates for the periods presented.

Impairment of ROU Assets and Leasehold Improvements

We are required to test for impairment of our long-lived assets when events arise that would call into question the recoverability of an asset group. We determined that the abandonment of our leased office space in Austin, Texas would meet this criteria. Accordingly, we tested for impairment using a discounted future cash flow model using estimated cash flows that could be obtained through a hypothetical sub-letting of the leased space.

Convertible Preferred Stock Issued through PIPE

We record shares of convertible preferred stock at their respective fair values on the dates of issuance, net of issuance costs. We classified the Series B Preferred Stock outside of stockholders' equity because, if conversion to common stock is not approved by the stockholders, the Series B Preferred Stock will be redeemable at the option of the holders for cash equal to the closing price of the common stock on the last trading day prior to the holder's redemption request. We determined that the conversion and redemption are outside of our control. Additionally, we determined the Series B Preferred Stock did not contain any embedded derivatives and therefore the conversion and redemption features did not require bifurcation.

Contingent Value Rights Liability

On July 3, 2023, we issued contingent value rights ("CVRs") to certain of our securityholders of record as of the close of business on that date (the "Legacy Stockholders"), but these were not issued to holders of shares of common stock or preferred stock issued to former stockholders of Pre-Merger Spyre or the investors (the "June 2023 Investors") in the June 2023 PIPE. Each CVR entitles the holder thereof to receive cash payments in the future calculated on the monetization or disposal of certain legacy assets owned by us prior to the Asset Acquisition (the "Legacy Assets") within the CVR period. Certain contingent payments under the CVR Agreement qualify as derivatives under ASC 815, Derivatives and Hedging, and are recorded as a liability on the balance sheet as of December 31, 2023. The CVR liability is considered a Level 3 instrument that is initially measured at its estimated fair value on the transaction date and subsequently remeasured at each reporting date with changes recorded in the consolidated statement of operations. The determination of the initial and subsequent fair value of the CVR liability requires significant judgment by management. Changes in any of the inputs not related to facts and circumstances existing as of the transaction date may result in a significant fair value adjustment, which can impact the results of operations in the period in which the adjustment is made. For example, changes in inputs related to the likelihood of regulatory approval increases or decreases as the regulatory approval process progresses and decisions or comments are issued by the applicable regulatory agencies.

Recently Issued Accounting Pronouncements

Information regarding recent accounting pronouncements is included in Item 8 of Part II, "Financial Statements and Supplementary Data", Note 2 in the "Notes to Consolidated Financial Statements" of this Annual Report.

Results of Operations

A discussion and analysis of our financial condition and results of operations for the year ended December 31, 2023 compared to the year ended December 31, 2022 is presented below. A discussion and analysis of our financial condition and results of operations for the year ended December 31, 2022 compared with the year ended December 31, 2021 is included in Item 7 of Part II, "Management's Discussion and Analysis

of Financial Condition and Results of Operations" in our Annual Report on Form 10-K for the year ended December 31, 2022 filed with the SEC on March 2, 2023.

Comparison of the Years Ended December 31, 2023 and 2022

The following table summarizes our results of operations for the years ended December 31, 2023 and 2022, together with the changes in those items in dollars and as a percentage:

	Year Ended December 31,		Dollar Change	% Change
	2023	2022		
	(in thousands)			
Revenue:				
Development fee and royalty	886	2,329	(1,443)	(62 %)
Total revenue	886	2,329	(1,443)	
Operating expenses:				
Research and development	89,504	58,579	30,925	53 %
General and administrative	39,946	28,531	11,415	40 %
Acquired in-process research and development	130,188	—	130,188	*
Gain on sale of in-process research and development asset	(16,449)	—	(16,449)	*
Total operating expenses	243,189	87,110	156,079	*
Loss from operations	(242,303)	(84,781)	(157,522)	*
Other (expense) income:				
Interest income	6,147	837	5,310	*
Change in fair value of forward contract liability	(83,530)	—	(83,530)	*
Other expense, net	(19,130)	(7)	(19,123)	*
Total other (expense) income	(96,513)	830	(97,343)	*
Loss before income tax expense	(338,816)	(83,951)	(254,865)	*
Income tax benefit	26	136	(110)	*
Net loss	$ (338,790)	$ (83,815)	$ (254,975)	

* Percentage not meaningful

Development Fee and Royalty Revenue. For the year ended December 31, 2023, we recognized $0.9 million of revenue in connection with the Immedica Agreement. The revenue generated was attributable to the PEACE Phase 3 trial and drug supply and royalties from an early access program in France. For the year ended December 31, 2022, we recognized $2.3 million of development fee revenue in connection with the Immedica Agreement, which was attributable to the PEACE Phase 3 trial and BLA package.

Research and Development Expenses. Our research and development expenses incurred during the year ended December 31, 2023 were primarily related to clinical trial costs associated with our Legacy Assets, costs associated with the wind down of those Legacy Assets, and costs associated with furthering our IBD pipeline candidates. Wind down costs included final patient visits, collection and analysis of final patient data, the creation and submission of final research reports, site and pharmacy closeouts, and formally closing the trials with regulatory agencies. Research and development expenses increased by $30.9 million, or 53%, to $89.5 million for the year ended December 31, 2023, from $58.6 million for the year ended December 31, 2022. The increase in research and development expenses was primarily due to:

- a $39.3 million increase in preclinical development and manufacturing expenses for our IBD pipeline candidates;

- a $11.4 million increase in stock compensation expense related to the Parapyre Option Obligation; partially offset by
- a $19.9 million decrease in activities and staff costs associated with the legacy rare disease pipeline we had been advancing prior to the Asset Acquisition.

External research and development expenses include costs associated with third parties contracted to conduct research and development activities on behalf of the Company, including through Paragon, CROs, CMOs, and third-party laboratories. For the year ended December 31, 2023 and 2022, external research and development costs accounted for $72.7 million and $36.4 million, respectively. The increase in external research and development expenses is primarily due to increases in costs associated with our IBD pipeline candidates and stock compensation expense related to the Parapyre Option Obligation, partially offset by a decrease in activities associated with the Legacy Assets.

Internal research and development expenses include compensation and related costs associated our research and development employees, as well as costs associated with the Company's on-premises research laboratory. For the year ended December 31, 2023 and 2022, internal research and development costs accounted for $16.8 million and $22.1 million. The decrease in internal research and development expenses is primarily due to a decrease in costs associated with our on-premises research laboratory that was decommissioned, including the elimination of related internal roles, in the first half of 2023.

General and Administrative Expenses. General and administrative expenses increased by $11.4 million, or 40%, to $39.9 million for the year ended December 31, 2023, from $28.5 million for the year ended December 31, 2022. The increase in general and administrative expenses was primarily due to a $9.0 million increase in stock compensation expense, $2.6 million increase in restructuring costs, net of restructuring savings, and an increase in legal and professional service fees of $3.4 million, partially offset by a $2.1 million decrease in legacy commercial readiness activities.

Gain on Sale of In-Process Research and Development Asset. Gain on sale of in-process research and development asset during the year ended December 31, 2023 was due to the gain recognized on the sale of pegzilarginase to Immedica. There was no similar gain or loss during the year ended December 31, 2022.

Acquired In-process Research and Development Expenses. Acquired IPR&D expenses were $130.2 million for the year ended December 31, 2023, as the acquisition of Pre-Merger Spyre was determined by management to be an asset acquisition, in accordance with U.S. GAAP as the product candidates were determined to have no alternative future use. There was no similar expense during the year ended December 31, 2022.

Change in Fair Value of Forward Contract Liability. Non-cash expenses associated with the change in fair value of the forward contract liability were $83.5 million for the year ended December 31, 2023. This expense was due to the change in fair value of the underlying Series A Preferred Stock between June 22, 2023 and the forward contract's settlement on July 7, 2023. There was no similar expense during the year ended December 31, 2022.

Liquidity and Capital Resources

We are a preclinical stage biotechnology company with a limited operating history, and due to our significant research and development expenditures, we have generated operating losses since our inception and have not generated any revenue from the sale of any products. There can be no assurance that profitable operations will ever be achieved, and, if achieved, whether profitability can be sustained on a continuing basis.

Since our inception and through December 31, 2023, we have funded our operations by raising an aggregate of approximately $896.2 million of gross proceeds from the sale and issuance of convertible preferred stock and common stock, pre-funded warrants, the collection of grant proceeds, and the licensing of our product rights for commercialization of pegzilarginase in Europe and certain countries in the Middle East. As of December 31, 2023, we had an accumulated deficit of $764.4 million.

Our primary use of cash is to fund the development of our product candidates, and advance our pipeline. This includes both the research and development costs and the general and administrative expenses required to support those operations. Since we are a preclinical stage biotechnology company, we have incurred significant operating losses since our inception and we anticipate such losses, in absolute dollar terms, to increase as we pursue clinical development of our product candidates, prepare for the potential commercialization of our product candidates, and expand our development efforts in our pipeline of nonclinical candidates. Based on current operating plans, the Company has sufficient resources to fund operations for at least one year from the issuance date of the financial statements included in this Annual Report with existing cash, cash equivalents, and marketable securities. Spyre will need to secure additional financing in the future to fund additional research and development, and before a commercial drug can be produced, marketed and sold. If the Company is unable to obtain additional financing or generate license or product revenue, the lack of liquidity could have a material adverse effect on the Company.

Recent sources of liquidity

In March 2021, we entered into the Immedica Agreement, pursuant to which Immedica licensed the product rights for commercialization of pegzilarginase in the European Economic Area, United Kingdom, Switzerland, Andorra, Monaco, San Marino, Vatican City, Turkey, Saudi Arabia, United Arab Emirates, Qatar, Kuwait, Bahrain, and Oman. In April 2021, we received an upfront payment of $21.5 million from Immedica. In July 2021, the Immedica Agreement was modified to include additional development services, up to $3.0 million, to support the PEACE Phase 3 trial and BLA package performance obligation. In July 2023, the Immedica Agreement was terminated through the sale of pegzilarginase to Immedica for $15.0 million in upfront cash proceeds and up to $100.0 million in contingent milestone payments.

During the year ended December 31, 2020, we raised $163.3 million of gross proceeds through an underwritten public offering and an at-the-market offering program. We sold 617,692 shares of common stock and pre-funded warrants to purchase up to 544,413 shares of common stock in an underwritten public offering for gross proceeds of $138.0 million, resulting in net proceeds of $129.0 million after deducting underwriting discounts, commissions, and offering costs. Additionally, we sold an aggregate of 129,803 shares of common stock under an at-the-market offering program for gross proceeds of $25.3 million, resulting in net proceeds of $24.6 million, after deducting underwriting discounts, commissions, and offering costs.

In May 2022, we sold 430,107 shares of common stock and pre-funded warrants to purchase up to 694,892 shares of common stock in a registered direct offering for gross proceeds of $45.0 million, resulting in net proceeds of $42.9 million after deducting placement agent fees and offering costs.

In June 2023, we sold 721,452 shares of convertible Series A preferred stock in a private placement offering for gross proceeds of $210.0 million before deducting approximately $12.7 million of placement agent and other offering expenses.

In December 2023, we sold 6,000,000 shares of Common Stock and 150,000 shares of convertible Series B preferred stock for gross proceeds of $180.0 million before deducting approximately $10.9 million of placement agent and other offering expenses.

Cash flows

The following table summarizes our cash flows for the periods indicated (in thousands):

	Year Ended December 31,	
	2023	2022
Net cash and cash equivalents (used in) provided by:		
Operating activities	$ (99,910)	$ (80,144)
Investing activities	(108,393)	57,008
Financing activities	361,077	42,678
Effect of exchange rate on cash, cash equivalents, and restricted cash	25	(106)
Net increase (decrease) in cash and cash equivalents	$ 152,799	$ 19,436

Cash Used in Operating Activities

Cash used in operating activities for the year ended December 31, 2023 was $99.9 million and reflected a net loss of $338.8 million. Our net loss was offset in part by non-cash expenses of $130.2 million for acquired IPR&D, $83.5 million change in fair value of forward contract liability, $25.7 million in stock-based compensation, $19.0 million change in fair value of CVR liability, $2.6 million impairment loss on lease abandonment, $0.9 million loss on disposal of long-lived assets, and $0.7 million in depreciation and amortization. The net change in operating assets and liabilities of $5.2 million was primarily due to a $4.9 million decrease in accrued and other liabilities, a $3.2 million decrease in prepaid expenses and other assets, a $2.4 million decrease in related party payable, a $2.3 million decrease in operating lease liabilities primarily due to the termination of the Las Cimas lease, and a $0.4 million decrease in development receivables, partially offset by a $0.6 million increase in deferred revenue and a $0.2 million increase in accounts payable.

Cash used in operating activities for the year ended December 31, 2022 was $80.1 million and reflected a net loss of $83.8 million. Our net loss was offset in part by non-cash expense of $7.1 million for stock-based compensation and $1.6 million for depreciation and amortization. The net change in operating assets and liabilities of $5.5 million was primarily related to a $2.6 million decrease in accounts payable, a $1.1 million increase in prepaid expenses and other assets, a $0.9 million decrease in deferred revenue due to receiving payments under the Immedica Agreement offset by the recognition of revenue allocated to the license, PEACE Phase 3 trial and BLA filing, a $0.9 million decrease in accrued expenses and other liabilities, and a $0.4 million decrease in operating lease liabilities due to lease payments made during the year, partially offset by a $0.4 million increase in accounts receivable for incremental services provided to Immedica and not yet paid.

Cash (Used in) Provided by Investing Activities

Cash used in investing activities for the year ended December 31, 2023 was $108.4 million and primarily consisted of $166.8 million in purchases of marketable securities, partially offset by $39.9 million in maturities and sales of marketable securities, $15.0 million in proceeds from the sale of IPR&D assets, and $3.0 million cash assumed from the Asset Acquisition.

Cash provided by investing activities for the year ended December 31, 2022 was $57.0 million and consisted of $96.5 million in maturities and sales of marketable securities, partially offset by $39.5 million in purchases of marketable securities.

Cash Provided by Financing Activities

Cash provided by financing activities for the year ended December 31, 2023 was $361.1 million, which primarily consisted of the net proceeds from the issuance of the shares of Series A Preferred Stock in the June 2023 PIPE and the issuance of the shares of common stock and Series B Preferred Stock in the December 2023 PIPE.

Cash provided by financing activities for the year ended December 31, 2022 was $42.7 million, which primarily consisted of $42.9 million from the registered direct offering of our common stock and pre-funded warrants in May 2022, net of placement agent fees and offering costs, and $0.2 million from the sale of common

stock under our 2016 Employee Stock Purchase Plan, partially offset by $0.4 million in principal payments made on our finance lease obligations.

Contractual Obligations and Other Commitments

Effective June 30, 2023, we abandoned our leased corporate headquarters and laboratory space located in Austin, Texas. As a result, we recognized an impairment loss related to the operating right-of-use asset of $0.9 million. On August 7, 2023, we terminated our building lease in Austin, Texas. In exchange for releasing us of all further obligations under the lease, we paid the lessor a $2.0 million termination fee.

We have entered into agreements in the normal course of business with CROs for clinical trials and CMOs, and with vendors for nonclinical research studies and other services and products for operating purposes. These contractual obligations are cancelable at any time by us, generally upon 30 to 60 days' prior written notice to the vendor.

Contingent contractual obligations

Through the Asset Acquisition, we received the Option to license the IPR&D related to four research programs. On July 12, 2023 and on December 14, 2023, we exercised the Option with respect to two of these research programs, respectively. The exercise of the Option allows for us to enter into an exclusive license agreement with Paragon for the respective research program. Upon license execution, we expect to be obligated to pay Paragon up to $22.0 million based on specific development, regulatory, and clinical milestones for each licensed research program. As of December 31, 2023, none of the $22.0 million obligation was accrued for since the related license agreements are still being negotiated. As of the date of the filing of this Annual Report, the Option remains unexercised with respect to the two remaining research programs under the Paragon Agreement. Should the Option for these research programs be exercised and upon entry into license agreements with respect to such research programs, we expect to be obligated to pay Paragon up to $22.0 million per research program based on certain development, regulatory, and clinical milestones.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

We are exposed to market risks in the ordinary course of our business. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of United States interest rates, particularly because our investments are in marketable securities. Our marketable securities are subject to interest rate risk and could fall in value if market interest rates increase. However, we believe that our exposure to interest rate risk is not significant as the majority of our investments are short-term in duration and have a low risk profile. A hypothetical 10% change in interest rates is not expected to have a material effect on the total market value of our investment portfolio. We have the ability to hold our marketable securities until maturity, and therefore, we would not expect our operating results or cash flows to be materially impacted by a change in market interest rates on our investments.

As of December 31, 2023, we held $339.6 million in cash, cash equivalents, marketable securities, and restricted cash, predominately all of which was denominated in U.S. dollars, and consisted primarily of investments in money market funds, commercial paper, U.S. government obligations, and corporate bonds.

We are also exposed to market risk related to changes in foreign currency exchange rates as a result of our entering into transactions denominated in currencies other than U.S. dollars. Due to the uncertain timing of expected payments in foreign currencies, we do not utilize any forward exchange contracts. All foreign transactions settle on the applicable spot exchange basis at the time such payments are made. For the twelve months ended December 31, 2023, a majority of our expenditures were denominated in U.S. dollars. A hypothetical 10% change in foreign exchange rates during any of the periods presented would not have had a material impact on our consolidated financial statements.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

SPYRE THERAPEUTICS, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

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

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Spyre Therapeutics, Inc. and its subsidiaries (the "Company") as of December 31, 2023 and 2022, and the related consolidated statements of operations, of comprehensive loss, of changes in convertible preferred stock and stockholders' equity and of cash flows for each of the three years in the period ended December 31, 2023, including the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2023 and 2022, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2023 in conformity with accounting principles generally accepted in the United States of America.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's consolidated 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 of these consolidated financial statements in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud. 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 consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matters

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

Contingent Value Right (CVR) Liability

As described in Notes 1, 2, 3, and 8 to the consolidated financial statements, in connection with the asset acquisition of Pre-Merger Spyre, a non-transferable contingent value right was distributed to certain legacy stockholders of record as of the close of business on July 3, 2023 entitling holders of the contingent value right to receive certain cash payments from proceeds received by the Company related to the disposition or monetization of the Company's legacy assets. Management determined that certain contingent payments under the Contingent Value Rights (CVR) Agreement qualified as derivatives, and as such, were recorded as a liability on the balance sheet. For derivative financial instruments accounted for as liabilities, the derivative instrument is initially recorded by management at its fair value and is then re-valued at each reporting date. The fair value of the CVR liability was determined using the probability weighted discounted cash flow method to estimate future cash flows associated with the sale of the legacy assets. The CVR liability value is based on significant inputs not observable in the market such as estimated cash flows, estimated probabilities of regulatory success,

estimated reimbursement rates compared to the reimbursement target, and risk-adjusted discount rates. The CVR liability as of December 31, 2023 was $42.7 million and the Company recognized an increase in the CVR liability of $19.0 million for the year ended December 31, 2023 related to the change in fair value between the issuance of the CVR and December 31, 2023.

The principal considerations for our determination that performing procedures relating to the valuation of the CVR liability is a critical audit matter are (i) the significant judgment by management when developing the fair value estimate of the CVR liability; (ii) a high degree of auditor judgment, subjectivity, and effort in performing procedures and evaluating management's significant assumptions related to the estimated probabilities of regulatory success, estimated reimbursement rates compared to the reimbursement target, and risk-adjusted discount rates; and (iii) the audit effort involved the use of professionals with specialized skill and knowledge.

Addressing the matter involved performing procedures and evaluating audit evidence in connection with forming our overall opinion on the consolidated financial statements. These procedures included, among others (i) reading and evaluating the terms of the CVR Agreement; (ii) testing management's process for developing the fair value estimate of the CVR liability; (iii) evaluating the appropriateness of the probability weighted discounted cash flow method used by management; (iv) testing the completeness and accuracy of underlying data used by management in the probability weighted discounted cash flow method; and (v) evaluating the reasonableness of the significant assumptions used by management related to the estimated probabilities of regulatory success, estimated reimbursement rates compared to the reimbursement target, and risk-adjusted discount rates. Evaluating management's assumptions related to estimated probabilities of regulatory success and estimated reimbursement rates compared to the reimbursement target involved evaluating whether the assumptions used by management were reasonable considering the consistency with (i) external market and industry data and (ii) evidence obtained in other areas of the audit. Professionals with specialized skill and knowledge were used to assist in evaluating (i) the appropriateness of the probability weighted discounted cash flow method and (ii) the reasonableness of the risk-adjusted discount rate assumption.

/s/ PricewaterhouseCoopers LLP
Austin, Texas
February 29, 2024

We have served as the Company's auditor since 2014.

Spyre Therapeutics, Inc.
Consolidated Balance Sheets
(In thousands, except share and per share amounts)

	December 31,	
	2023	2022
ASSETS		
CURRENT ASSETS		
Cash and cash equivalents	$ 188,893	$ 34,863
Marketable securities	150,384	20,848
Development receivables	—	375
Prepaid expenses and other current assets	2,251	6,172
Total current assets	341,528	62,258
Restricted cash	322	1,553
Property and equipment, net	—	3,220
Operating lease right-of-use assets	—	3,430
Other non-current assets	9	683
TOTAL ASSETS	$ 341,859	$ 71,144
LIABILITIES AND STOCKHOLDERS' EQUITY		
CURRENT LIABILITIES		
Accounts payable	$ 896	$ 677
CVR liability	1,390	—
Operating lease liabilities	—	625
Deferred revenue	—	517
Accrued and other current liabilities	13,108	12,837
Related party accounts payable and other current liabilities	16,584	—
Total current liabilities	31,978	14,656
Non-current CVR liability	41,310	—
Non-current operating lease liabilities	—	4,004
Deferred revenue, net of current portion	—	2,179
TOTAL LIABILITIES	73,288	20,839
Commitments and Contingencies (Note 9)		
Series B non-voting convertible preferred stock, $0.0001 par value; 150,000 and no shares authorized as of December 31, 2023 and December 31, 2022, respectively; 150,000 and no shares issued and outstanding as of December 31, 2023 and December 31, 2022, respectively.	84,555	—
STOCKHOLDERS' EQUITY		
Series A non-voting convertible preferred stock, $0.0001 par value; 1,086,341 and no shares authorized as of December 31, 2023 and December 31, 2022, respectively; 437,037 and no shares issued and outstanding as of December 31, 2023 and December 31, 2022, respectively.	184,927	—
Preferred stock, $0.0001 par value; 8,763,659 shares and 10,000,000 authorized as of December 31, 2023 and December 31, 2022, respectively; no shares issued and outstanding as of December 31, 2023 and December 31, 2022.	—	—
Common stock, $0.0001 par value; 400,000,000 and 20,000,000 shares authorized as of December 31, 2023 and December 31, 2022, respectively; 36,057,109 shares and 2,614,014 shares issued and outstanding as of December 31, 2023 and December 31, 2022, respectively.	10	6
Additional paid-in capital	763,191	475,971
Accumulated other comprehensive income (loss)	302	(48)
Accumulated deficit	(764,414)	(425,624)
TOTAL STOCKHOLDERS' EQUITY	184,016	50,305
TOTAL LIABILITIES, CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY	$ 341,859	$ 71,144

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

Spyre Therapeutics, Inc.
Consolidated Statements of Operations
(In thousands, except share and per share amounts)

	Year Ended December 31,		
	2023	**2022**	**2021**
Revenue:			
License	$ —	$ —	$ 12,000
Development fee and royalty	886	2,329	6,739
Total revenue	886	2,329	18,739
Operating expenses:			
Research and development [(1)]	89,504	58,579	57,069
General and administrative	39,946	28,531	27,319
Acquired in-process research and development	130,188	—	—
Gain on sale of in-process research and development asset	(16,449)	—	—
Total operating expenses	243,189	87,110	84,388
Loss from operations	(242,303)	(84,781)	(65,649)
Other (expense) income:			
Interest income	6,147	837	111
Change in fair value of forward contract liability	(83,530)	—	—
Other expense, net	(19,130)	(7)	(122)
Total other (expense) income	(96,513)	830	(11)
Loss before income tax expense	(338,816)	(83,951)	(65,660)
Income tax benefit (expense)	26	136	(141)
Net loss	$ (338,790)	$ (83,815)	$ (65,801)
Net loss per share, basic and diluted	$ (49.12)	$ (24.86)	$ (25.02)
Weighted-average common shares outstanding, basic and diluted	6,897,065	3,371,231	2,629,784

(1) Includes $48.5 million in related party expenses for the year ended December 31, 2023 and no related party expenses for the year ended months ended December 31, 2022 and 2021.

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

Spyre Therapeutics, Inc.
Consolidated Statements of Comprehensive Loss
(In thousands)

	Year Ended December 31,		
	2023	2022	2021
Net loss	$ (338,790)	$ (83,815)	$ (65,801)
Other comprehensive income (loss):			
Foreign currency translation adjustment	37	(35)	(1)
Unrealized gain (loss) on marketable securities	313	7	(30)
Total comprehensive loss	$ (338,440)	$ (83,843)	$ (65,832)

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

Spyre Therapeutics, Inc.
Consolidated Statements of Changes in Convertible Preferred Stock and Stockholders' Equity
(In thousands)

	Series B Non-Voting Convertible Preferred Stock		Series A Non-Voting Convertible Preferred Stock		Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive (Loss) Income	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount	Shares	Amount	Shares	Amount				
Balances—December 31, 2020	—	$ —	—	$ —	1,918	$ 5	$ 415,824	$ 11	$ (276,008)	$ 139,832
Issuance of common stock in connection with exercise of pre-funded warrants	—	—	—	—	40	—	—	—	—	—
Issuance of common stock in connection with exercise of stock options and employee stock purchase plan	—	—	—	—	16	—	1,903	—	—	1,903
Stock-based compensation expense	—	—	—	—	—	—	8,038	—	—	8,038
Foreign currency translation adjustment	—	—	—	—	—	—	—	(1)	—	(1)
Unrealized loss on marketable securities	—	—	—	—	—	—	—	(30)	—	(30)
Net loss	—	—	—	—	—	—	—	—	(65,801)	(65,801)
Balances—December 31, 2021	—	$ —	—	$ —	1,974	$ 5	$ 425,765	$ (20)	$ (341,809)	$ 83,941
Issuance of common stock and pre-funded warrants in connection with registered direct offering, net of offering costs	—	—	—	—	430	1	42,873	—	—	42,874
Issuance of common stock in connection with exercise of pre-funded warrants	—	—	—	—	204	—	—	—	—	—
Issuance of common stock in connection with employee stock purchase plan	—	—	—	—	6	—	222	—	—	222
Stock-based compensation expense	—	—	—	—	—	—	7,111	—	—	7,111
Foreign currency translation adjustment	—	—	—	—	—	—	—	(35)	—	(35)
Unrealized gain on marketable securities	—	—	—	—	—	—	—	7	—	7
Net loss	—	—	—	—	—	—	—	—	(83,815)	(83,815)
Balances—December 31, 2022	—	$ —	—	$ —	2,614	$ 6	$ 475,971	$ (48)	$ (425,624)	$ 50,305
Issuance of Series A non-voting convertible preferred stock in connection with private placement, net of financing costs	—	—	721	197,364	—	—	—	—	—	197,364
Issuance of Series A non-voting convertible preferred stock in connection with the asset acquisition of Spyre and settlement of related forward contract	—	—	365	189,741	—	—	—	—	—	189,741
Conversion of Series A non-voting convertible preferred stock into common stock	—	—	(649)	(202,178)	25,972	3	202,175	—	—	—
Issuance of Series B non-voting convertible preferred stock in connection with private placement, net of financing costs	150	84,555	—	—	—	—	—	—	—	—
Issuance of common stock in connection with private placement, net of financing costs	—	—	—	—	6,000	—	84,555			84,555
Issuance of common stock in connection with the asset acquisition of Spyre	—	—	—	—	518	1	3,767			3,768
Issuance of common stock in connection with exercise of pre-funded warrants	—	—	—	—	905	—	—	—	—	—
Issuance of common stock in connection with exercise of stock options and employee stock purchase plan	—	—	—	—	48	—	405	—	—	405
CVR distribution to common stockholders	—	—	—	—	—	—	(29,500)	—	—	(29,500)
Stock-based compensation expense	—	—	—	—	—	—	14,347	—	—	14,347
Issuance of Parapyre Option Obligation warrants —	—	—	—	—	—	—	11,471	—	—	11,471
Foreign currency translation adjustment	—	—	—	—	—	—	—	37	—	37
Unrealized gain on marketable securities	—	—	—	—	—	—	—	313	—	313
Net loss	—	—	—	—	—	—	—	—	(338,790)	(338,790)
Balances—December 31, 2023	150	$ 84,555	437	$ 184,927	36,057	$ 10	$ 763,191	$ 302	$ (764,414)	$ 184,016

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

Spyre Therapeutics, Inc.
Consolidated Statements of Cash Flows
(In thousands)

	Year Ended December 31,		
	2023	2022	2021
CASH FLOWS FROM OPERATING ACTIVITIES			
Net loss	$ (338,790)	$ (83,815)	$ (65,801)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	744	1,567	1,576
Stock-based compensation	25,675	7,111	8,038
Acquired in-process research and development	130,188	—	—
Change in fair value of CVR liability	18,986	—	—
Change in fair value of forward contract liability	83,530	—	—
Gain on sale of in-process research and development asset	(16,449)	—	—
Lease ROU asset and leasehold improvement impairment loss	2,580	—	—
Loss on disposal of long-lived assets	915	—	—
Net (accretion of discount) amortization of premium on marketable securities	(2,318)	(327)	548
Amortization of operating lease assets	220	397	425
Other	15	426	(335)
Changes in operating assets and liabilities:			
Prepaid expenses and other assets	3,245	(1,144)	(1,216)
Accounts payable	218	(2,641)	1,065
Deferred revenue	575	(880)	3,576
Development receivables	375	440	(815)
Operating lease liabilities	(2,326)	(435)	(404)
Accrued and other liabilities	(4,891)	(843)	(373)
Related party payable	(2,402)	—	—
Net cash used in operating activities	(99,910)	(80,144)	(53,716)
CASH FLOWS FROM INVESTING ACTIVITIES			
Cash assumed from asset acquisition of Spyre	3,035	—	—
Proceeds from sale of in-process research & development asset	15,000	—	—
Purchases of property and equipment	—	(38)	(573)
Proceeds from the sale of property plant and equipment	475	—	—
Purchases of marketable securities	(166,803)	(39,500)	(133,079)
Proceeds from maturities and sales of marketable securities	39,900	96,546	111,033
Net cash provided by (used in) investing activities	(108,393)	57,008	(22,619)
CASH FLOWS FROM FINANCING ACTIVITIES			
Proceeds from issuance of Series A non-voting convertible preferred stock in connection with private placement, net of placement and other offering costs	197,364	—	—
Proceeds from issuance of Series B non-voting convertible preferred stock in connection with private placement, net of placement and other offering costs	84,555	—	—
Proceeds from issuance of common stock in connection with private placement, net of placement and other offering costs	84,555	—	—
Payment of contingent value rights liability	(5,786)	—	—
Proceeds from issuance of common stock and pre-funded warrants in registered direct offering, net of offering costs	—	42,874	—
Proceeds from employee stock plan purchases and stock option exercises	405	222	1,903
Principal payments on finance lease obligation	(16)	(418)	(510)
Net cash provided by financing activities	361,077	42,678	1,393
Effect of exchange rate on cash, cash equivalents, and restricted cash	25	(106)	(15)
NET INCREASE (DECREASE) IN CASH, CASH EQUIVALENTS, AND RESTRICTED CASH	152,799	19,436	(74,957)
CASH, CASH EQUIVALENTS, AND RESTRICTED CASH			
Beginning of period	36,416	16,980	91,937
End of period	$ 189,215	$ 36,416	$ 16,980
Supplemental Disclosure of Non-Cash Investing and Financing Information:			
Settlement of forward contract liability and issuance of Series A non-voting convertible preferred stock in connection with the asset acquisition of Spyre	$ 189,741	$ —	$ —
Conversion of Series A non-voting convertible preferred stock into common stock	$ 202,178	$ —	$ —
Leased assets obtained in exchange for lease obligations	$ —	$ 21	$ 872

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

Spyre Therapeutics, Inc.
Notes to Consolidated Financial Statements

1. The Company and Basis of Presentation

Spyre Therapeutics, Inc., formerly Aeglea BioTherapeutics, Inc., (“Spyre” or the “Company”) is a preclinical stage biotechnology company focused on developing next generation therapeutics for patients living with inflammatory bowel disease. The Company was formed as a Limited Liability Company ("LLC") in Delaware on December 16, 2013 under the name Aeglea BioTherapeutics Holdings, LLC and was converted from a Delaware LLC to a Delaware corporation on March 10, 2015. On November 27, 2023, the Company completed its corporate rebranding, changing the name of the Company to Spyre Therapeutics, Inc. The Company operates in one segment and has its principal offices in Waltham, Massachusetts.

On September 8, 2023, the Company effected a reverse stock split of its Common Stock at a ratio of 1-for-25 (the “Reverse Split”). Except as indicated otherwise, all share numbers related to the Company's Common Stock disclosed in these financial statements have been adjusted on a post-Reverse Split basis.

On April 12, 2023, based on the review of the inconclusive interim results from the Company's Phase 1/2 clinical trial of pegtarviliase for the treatment of Classical Homocystinuria and other business considerations, the Company announced that it had initiated a process to explore strategic alternatives to maximize stockholder value and engaged an independent exclusive financial advisor to support this process. As a result, in April 2023, the Company implemented a restructuring plan resulting in an approximate 83% reduction of the Company’s existing headcount.

On June 22, 2023, the Company acquired, in accordance with the terms of the Agreement and Plan of Merger (the "Acquisition Agreement"), the assets of Spyre Therapeutics, Inc. (“Pre-Merger Spyre”) as disclosed in Note 7 and 8, a privately held biotechnology company advancing a pipeline of antibody therapeutics with the potential to transform the treatment of inflammatory bowel disease through a research and development option agreement ("Paragon Agreement") with Paragon Therapeutics ("Paragon"). The asset acquisition was accomplished through a two-step reverse triangular merger whereby a wholly owned subsidiary of the Company merged with and into Pre-Merger Spyre, which existed at the time the Acquisition Agreement was entered into, became a wholly owned subsidiary of the Company in accordance with the terms of the Acquisition Agreement. Immediately following this merger, Pre-Merger Spyre merged with an into a second wholly subsidiary of the Company (“Merger Sub”) in accordance with the terms of the Acquisition Agreement and Pre-Merger Spyre ceased to exist. Subsequently, Aeglea BioTherapeutics, Inc. was renamed Spyre Therapeutics, Inc. and is a different entity than Pre-Merger Spyre, which ceased to exist upon merging with Merger Sub. The transaction was structured as a stock-for-stock transaction pursuant to which all of Pre-Merger Spyre's outstanding equity interests were exchanged based on a fixed exchange ratio of 0.5494488 to 1 for consideration from the Company of 517,809 shares of common stock and 364,887 shares of Series A non-voting convertible preferred stock, par value of $0.0001 per share ("Series A Preferred Stock") (convertible on a 40 to 1 basis), in addition to the assumption of outstanding and unexercised stock options to purchase 2,734 shares of common stock from the Amended and Restated Spyre 2023 Equity Incentive Plan (the "Asset Acquisition"). The common stock and Series A Preferred Stock related to the Asset Acquisition were issued to the Pre-Merger Spyre stockholders on July 7, 2023. For additional information, see Note 8.

In connection with the Asset Acquisition, on June 26, 2023, the Company completed a private placement of shares of Series A Preferred Stock (the “Series A PIPE”) to a group of investors (the “Series A Investors”). The Company sold an aggregate of 721,452 shares of Series A Preferred Stock (the “Series A PIPE Securities”) for an aggregate purchase price of approximately $210.0 million before deducting approximately $12.7 million of placement agent and other offering expenses. For additional information, see Note 11.

In connection with the Asset Acquisition, a non-transferable contingent value right ("CVR") was distributed to stockholders of record of the Company as of the close of business on July 3, 2023 (the "Legacy Stockholders"), but was not distributed to the holders of shares of common stock or Series A Preferred Stock issued to the former stockholders of Pre-Merger Spyre or Investors in the Transactions. Holders of the CVRs will be entitled to receive cash payments from proceeds received by the Company for a 3-year period related to the disposition or monetization of its legacy assets for a period of one-year following the closing of the Asset Acquisition. For additional information, see Note 3.

On November 21, 2023, the Company's stockholders approved the conversion of the Company's Series A non-voting convertible preferred stock to Common Stock. For additional information, see Note 11.

On December 11, 2023, the Company completed a private placement of shares of common stock and Series B non-voting convertible preferred stock, par value of $0.0001 per share ("Series B Preferred Stock") (convertible on a 40 to 1 basis) (collectively, the “December 2023 PIPE”) to a group of investors (the “December 2023 PIPE Investors”). The Company sold an aggregate of 6,000,000 shares of Common Stock and 150,000 shares of Series B Preferred Stock (the “December 2023 PIPE Securities”) for an aggregate purchase price of approximately $180.0 million before deducting approximately $10.9 million of placement agent and other offering expenses. For additional information, see Note 11.

Liquidity

The Company is a preclinical stage biotechnology company with a limited operating history, and due to its significant research and development expenditures, the Company has generated operating losses since its inception and has not generated any revenue from the commercial sale of any products. There can be no assurance that profitable operations will ever be achieved, and, if achieved, whether profitability can be sustained on a continuing basis.

Since its inception and through December 31, 2023, the Company has funded our operations by raising an aggregate of approximately $896.2 million of gross proceeds from the sale and issuance of convertible preferred stock and common stock, pre-funded warrants, the collection of grant proceeds, and the licensing of its product rights for commercialization of pegzilarginase in Europe and certain countries in the Middle East. As of December 31, 2023, Spyre had an accumulated deficit of $764.4 million, and cash, cash equivalents, and marketable securities of $339.3 million.

Based on current operating plans, the Company has sufficient resources to fund operations for at least one year from the issuance date of these financial statements with existing cash, cash equivalents, and marketable securities. Spyre will need to secure additional financing in the future to fund additional research and development, and before a commercial drug can be produced, marketed and sold. If the Company is unable to obtain additional financing or generate license or product revenue, the lack of liquidity could have a material adverse effect on the Company.

Basis of Presentation

The consolidated financial statements have been prepared in conformity with generally accepted accounting principles in the United States (“U.S. GAAP”) as defined by the Financial Accounting Standards Board (“FASB”) and include the accounts of the Company and its wholly owned subsidiaries. All intercompany balances and transactions have been eliminated in consolidation.

2. Summary of Significant Accounting Policies

Use of Estimates

The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and accompanying notes. Management bases its estimates on historical experience and on various other market-specific and relevant assumptions that management believes to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets, liabilities, and equity and the amount of revenues and expenses. Actual results could differ significantly from those estimates. The most significant estimates and assumptions that management considers in the preparation of the Company's financial statements relate to the valuation of consideration transferred in acquiring in-process research & development ("IPR&D"); the discount rate, probabilities of success, and timing of estimated cash flows in the valuation of the CVR liability; inputs used in the Black-Scholes model for stock-based compensation expense; estimated future cash flows used in calculating the impairment of right-of-use lease assets; and estimated cost to complete performance obligations related to revenue recognition. The consideration transferred in acquiring IPR&D in connection with the acquisition of Pre-Merger Spyre was comprised of shares of the Company’s Common Stock and shares of Series A Preferred Stock. To determine the fair value of the equity transferred, the Company considered the per share value of the Series A PIPE securities, which was a financing event involving a group of accredited investors.

Cash and Cash Equivalents

The Company considers all highly liquid investments with original maturities of three months or less from the date of purchase to be cash equivalents. Cash equivalents consist of money market funds and debt securities and are stated at fair value.

Marketable Securities

All investments have been classified as available-for-sale and are carried at estimated fair value as determined based upon quoted market prices or pricing models for similar securities. Management determines the appropriate classification of its investments in debt securities at the time of purchase. The Company may hold securities with stated maturities greater than one year until maturity. All available-for-sale securities are considered available to support current operations and are classified as current assets. The Company presents credit losses as an allowance rather than as a reduction in the amortized cost of the available-for-sale securities.

For available-for-sale debt securities in an unrealized loss position, the Company first assesses whether it intends to sell, or it is more likely than not that it will be required to sell the security before recovery of its amortized cost basis. If either of the criteria regarding intent or requirement to sell is met, the security's amortized cost basis is written down to fair value and recognized in other income (expense) in the results of operations. For available-for-sale debt securities that do not meet the aforementioned criteria, the Company evaluates whether the decline in fair value has resulted from credit losses or other factors. In making this assessment, management considers the extent to which fair value is less than amortized cost, any changes to the rating of the security by a rating agency, and adverse conditions specifically related to the security, among other factors. If this assessment indicates that a credit loss exists, an allowance is recorded for the difference between the present value of cash flows expected to be collected and the amortized cost basis of the security. Impairment losses attributable to credit loss factors are charged against the allowance when management believes an available-for-sale security is uncollectible or when either of the criteria regarding intent or requirement to sell is met.

Any unrealized losses from declines in fair value below the amortized cost basis as a result of non-credit loss factors is recognized as a component of accumulated other comprehensive (loss) income, along with unrealized gains. Realized gains and losses and declines in fair value, if any, on available-for-sale securities are included in other income (expense) in the results of operations. The cost of securities sold is based on the specific-identification method.

Restricted Cash

Restricted cash consisted of money market accounts held by financial institutions as collateral for the Company's obligations under a credit agreement and a facility lease for the Company's corporate headquarters in Austin, Texas. The lease was terminated in August 2023 and the cash was subsequently unrestricted. Remaining restricted cash balances relate to the Company's operations in the United Kingdom.

Concentration of Credit Risk

Financial instruments that potentially subject the Company to a concentration of credit risk consist of cash, cash equivalents, marketable securities, and restricted cash. The Company's investment policy limits investments to high credit quality securities issued by the U.S. government, U.S. government-sponsored agencies, highly rated banks, and corporate issuers, subject to certain concentration limits and restrictions on maturities. The Company's cash, cash equivalents, marketable securities, and restricted cash are held by financial institutions that management believes are of high credit quality. The financial instruments that potentially subject the Company to a concentration of credit risk consist principally of cash deposits. Accounts at each of the Company's two U.S. banking institutions are insured by the Federal Deposit Insurance Corporation ("FDIC") up to $250,000 per depositor. As of December 31, 2023 and 2022, balances at the Company's U.S. banking institutions exceeded the FDIC limits. The Company has not experienced any losses on its deposits of cash, cash equivalents, and restricted cash and its accounts are monitored by management to mitigate risk. The Company is exposed to credit risk in the event of default by the financial institutions holding its cash, cash equivalents, and restricted cash, and bond issuers.

Property and Equipment

Property and equipment are stated at cost, net of accumulated depreciation and amortization. Depreciation and amortization are computed using the straight-line method over the estimated useful lives of the assets. Repairs and maintenance that do not extend the life or improve an asset are expensed as incurred. Upon retirement or sale, the cost of disposed assets and their related accumulated depreciation and amortization are removed from the balance sheet. Any gain or loss is credited or charged to operations.

The useful lives of the property and equipment are as follows:

Laboratory equipment	5 years
Furniture and office equipment	5 years
Computer equipment	3 years
Software	3 years
Leasehold improvements	Shorter of remaining lease term or estimated useful life

Impairment of Long-Lived Assets

Long-lived assets are reviewed for indications of possible impairment whenever events or changes in circumstances indicate that the carrying amount of an asset may not be recoverable. Recoverability is measured by comparison of the carrying amounts to the future undiscounted cash flows attributable to these assets. An impairment loss is recognized to the extent an asset group is not recoverable, and the carrying amount exceeds the fair value. The Company recognized a $2.6 million impairment loss for the year ended December 31, 2023 related to its leased office space in Austin, Texas (see Note 17 for additional information). There were no impairments of long-lived assets for the years ended December 31, 2022 and 2021.

Accrued Research and Development Costs

The Company records the costs associated with research nonclinical studies, clinical trials, and manufacturing development as incurred. These costs are a significant component of the Company’s research and development expenses, with a substantial portion of the Company’s on-going research and development activities conducted by third-party service providers, including contract research organizations ("CROs") and contract manufacturing organizations ("CMOs"), and the Company's related-party Paragon.

The Company accrues for expenses resulting from obligations under the Paragon Agreement and agreements with CROs, CMOs, and other outside service providers for which payment flows do not match the periods over which materials or services are provided to the Company. Accruals are recorded based on estimates of services received and efforts expended pursuant to agreements established with Paragon, CROs, CMOs, and other outside service providers. These estimates are typically based on contracted amounts applied to the proportion of work performed and determined through analysis with internal personnel and external service providers as to the progress or stage of completion of the services. The Company makes significant judgments and estimates in determining the accrual balance in each reporting period. In the event advance payments are made to Paragon, a CRO, CMO, or outside service provider, the payments will be recorded as a prepaid asset which will be amortized as the contracted services are performed. As actual costs become known, the Company adjusts its accruals. Inputs, such as the services performed, the number of patients enrolled, or the study duration, may vary from the Company’s estimates, resulting in adjustments to research and development expense in future periods. Changes in these estimates that result in material changes to the Company’s accruals could materially affect the Company’s results of operations. Historically, the Company has not experienced any material deviations between accrued and actual research and development expenses.

Leases

The Company determines if an arrangement is a lease at inception. Right-of-use ("ROU") assets represent the Company's right to use an underlying asset for the lease term and lease liabilities represent the Company's obligation to make lease payments arising from the lease. The classification of the Company's leases as operating or finance leases along with the initial measurement and recognition of the associated ROU assets and lease liabilities is performed at the lease commencement date. The measurement of lease liabilities

is based on the present value of future lease payments over the lease term. As the Company's leases do not provide an implicit rate, the Company uses its incremental borrowing rate based on the information available at the lease commencement date in determining the present value of future lease payments. To determine the incremental borrowing rate, the Company uses the lease-term appropriate current treasury bond rates adjusted for collateral and inflation risks combined with quoted bank financing rates. The ROU asset is based on the measurement of the lease liability and also includes any lease payments made prior to or on lease commencement and excludes lease incentives and initial direct costs incurred, as applicable. The lease terms may include options to extend or terminate the lease when it is reasonably certain the Company will exercise any such options. Rent expense for the Company's operating leases is recognized on a straight-line basis over the lease term. Amortization expense for the ROU asset associated with its finance leases is recognized on a straight-line basis over the term of the lease and interest expense associated with its finance leases is recognized on the balance of the lease liability using the effective interest method based on the estimated incremental borrowing rate.

Prior to the Company's restructuring, as described in Note 17, the Company had lease agreements with lease and non-lease components. As allowed under Topic 842, the Company elected to not separate lease and non-lease components for any leases involving real estate and office equipment classes of assets and, as a result, accounted for the lease and non-lease components as a single lease component. The Company also elected to not apply the recognition requirement of Topic 842 to leases with a term of 12 months or less for all classes of assets.

Fair Value of Financial Instruments

The Company uses fair value measurements to record fair value adjustments to certain financial and non-financial assets and liabilities and to determine fair value disclosures. The accounting standards define fair value, establish a framework for measuring fair value, and require disclosures about fair value measurements. Fair value is defined as the price that would be received from selling an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. When determining the fair value measurements for assets and liabilities required to be recorded at fair value, the principal or most advantageous market in which the Company would transact are considered along with assumptions that market participants would use when pricing the asset or liability, such as inherent risk, transfer restrictions, and risk of nonperformance.

The accounting standard for fair value establishes a fair value hierarchy based on three levels of inputs, the first two of which are considered observable and the last unobservable, that requires an entity to maximize the use of observable inputs and minimize the use of unobservable inputs when measuring fair value. A financial instrument’s categorization within the fair value hierarchy is based upon the lowest level of input that is significant to the fair value measurement.

The three levels of inputs that may be used to measure fair value are as follows:

Level 1: Observable inputs, such as quoted prices in active markets for identical assets or liabilities.

Level 2: Observable inputs other than Level 1 prices, such as quoted prices for similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.

Level 3: Valuations based on unobservable inputs to the valuation methodology and including data about assumptions that market participants would use in pricing the asset or liability based on the best information available under the circumstances.

Financial instruments carried at fair value include cash equivalents and marketable securities. The carrying amounts of accounts payable and accrued liabilities approximate fair value due to their relatively short maturities.

Revenue Recognition

Under ASC Topic 606, "Revenue from Contracts with Customers" ("Topic 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. To determine revenue recognition for arrangements that an entity determines are within the scope of Topic 606, the entity performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price, including variable consideration, if any; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation.

The Company assesses its license arrangements within the scope of Topic 606 in accordance with this framework as follows:

License revenue

The Company assesses whether the goods or services promised within each contract are distinct to identify those that are performance obligations. This assessment involves subjective determinations and requires management to make judgments about the individual promised goods or services and whether such are separable from the other aspects of the contractual relationship. In assessing whether a promised good or service is distinct, and therefore a performance obligation, the Company considers factors such as the research, stage of development of the licensed product, manufacturing and commercialization capabilities of the customer and the availability of the associated expertise in the general 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 a promised good or service is not distinct, the Company is required to combine that good or service with other promised goods or services until it identifies a bundle of goods or services that is distinct. Arrangements that include rights to additional goods or services that are exercisable at a customer's discretion are generally considered options. The Company assesses if these options provide a material right to the customer and if so, they are considered performance obligations.

The transaction price is determined and allocated to the identified performance obligations in proportion to their stand-alone selling prices ("SSP") on a relative SSP basis. SSP is based on observable prices of the performance obligations or, when such prices are not observable, are estimated. The estimation of SSP may include factors such as forecasted revenues or costs, development timelines, discount rates, probabilities of technical and regulatory success, and considerations such as market conditions and entity-specific factors. In certain circumstances, the Company may apply the residual method to determine the SSP of a good or service if the SSP is considered highly variable or uncertain. The Company validates the SSP for performance obligations by evaluating whether changes in the key assumptions used to determine the SSP will have a significant effect on the allocation of arrangement consideration between multiple performance obligations.

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 amount of estimated variable consideration in the transaction price to the extent that 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 its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis in the period of adjustment.

If an arrangement includes development, regulatory or commercial milestone payments, the Company evaluates whether the milestones are considered likely 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 cumulative revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the Company's control or the licensee's control, such as regulatory approvals, are generally not considered likely of being achieved until those approvals are received.

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

does not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the licensee and the transfer of the promised goods or services to the licensees will be one year or less. For arrangements with licenses of intellectual property that include sales-based royalties, including milestone payments based on the level of sales, and if 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.

The Company recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) each performance obligation is satisfied at a point in time or over time, and if over time, recognition is based on the use of an output or input method.

The Company's contracts may be modified for changes in the customer's requirements. If contract modifications are for additional goods and services that are distinct from the existing contract, the modification will be accounted for as either a separate contract or a termination of the existing contract, depending on whether the additional goods or services reflects the SSP.

If the additional goods or services in a contract modification are not distinct from the existing contract, they are accounted for as if they were part of the original contract. The effect of the contract modification on the transaction price and the measure of progress for the performance obligation to which it relates is recognized as an adjustment to revenue on a cumulative catch-up basis. The cumulative catch-up adjustment is calculated using an updated measure of progress applied to the sum of (1) the remaining consideration allocated to the partially satisfied performance obligation and (2) the revenue already recognized on that performance obligation. The revenue recognized for fully satisfied goods or services and distinct from the remaining performance obligations is not altered by the modification.

Collaborative arrangements

The Company analyzes its license arrangements to assess whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and 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 ("Topic 808"). This assessment is performed throughout the life of the arrangement based on changes in the responsibilities of all parties in the arrangement. For arrangements within the scope of Topic 808 that contain multiple elements, the Company first determines which elements of the collaboration are deemed to be within the scope of Topic 808 and which elements of the collaboration are more reflective of a vendor-customer relationship and therefore within the scope of Topic 606. For elements of collaboration arrangements that are accounted for pursuant to Topic 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. For those elements of the arrangement that are accounted for pursuant to Topic 606, the Company applies the five-step model described above.

Research and Development Costs

Research and development costs are expensed as incurred. Research and development costs include, but are not limited to, salaries, benefits, travel, stock-based compensation, consulting costs, contract research service costs, laboratory supplies and facilities, contract manufacturing costs, and costs paid to other third parties that conduct research and development activities on the Company's behalf. Amounts incurred in connection with license agreements are also included in research and development expense.

Advance payments for goods or services to be rendered in the future for use in research and development activities are recorded as a prepaid asset and expensed as the related goods are delivered or the services are performed.

Stock-Based Compensation

The Company recognizes the cost of stock-based awards granted to employees and non-employees based on the estimated grant-date fair values of the awards. The fair values of stock options are estimated on the date of grant using the Black-Scholes option pricing model. The fair values of restricted stock units ("RSUs") are based on the fair value of the Company's common stock on the date of the grant. The value of the award is

recognized as compensation expense on a straight-line basis over the requisite service period. Forfeitures are recognized when they occur, which may result in the reversal of compensation costs in subsequent periods as the forfeitures arise. Compensation expense for employee and non-employee share-based payment awards with performance conditions is recognized when the performance condition is deemed probable.

Convertible Preferred Stock Issued through PIPE

The Company records shares of convertible preferred stock at their respective fair values on the dates of issuance, net of issuance costs. The Company classified the Series B Preferred Stock outside of stockholders' equity because, if conversion to Common Stock is not approved by the stockholders, the Series B Preferred Stock will be redeemable at the option of the holders for cash equal to the closing price of the Common Stock on the last trading day prior to the holder's redemption request. The Company has determined that the conversion and redemption are outside of the Company's control. Additionally, the Company determined the Series B Preferred Stock did not contain any embedded derivatives and therefore the conversion and redemption features did not require bifurcation.

Contingent Milestone Proceeds

The Company recognizes contingent milestone proceeds associated from the sale of in-process research and development assets in earnings once the achievement of the milestone becomes probable and payment to the Company is contractually required.

Acquisitions

The Company evaluates acquisitions of assets and other similar transactions to assess whether or not the transaction should be accounted for as a business combination or asset acquisition by first applying a screen test to determine whether substantially all of the fair value of the gross assets acquired is concentrated in a single identifiable asset or group of similar identifiable assets. If so, the transaction is accounted for as an asset acquisition. If not, further determination is required as to whether or not the Company has acquired inputs and processes that have the ability to create outputs, which would meet the definition of a business. Significant judgment is required in the application of the test to determine whether an acquisition is a business combination or an acquisition of assets.

Acquisitions meeting the definition of business combinations are accounted for using the acquisition method of accounting, which requires that the purchase price be allocated to the net assets acquired at their respective fair values. In a business combination, any excess of the purchase price over the estimated fair values of the net assets acquired is recorded as goodwill.

The Company measures and recognizes asset acquisitions that are not deemed to be business combinations based on the cost to acquire the assets, which includes pre-acquisition direct costs recorded in accrued professional and consulting fees. Goodwill is not recognized in asset acquisitions. When a transaction accounted for as an asset acquisition includes an IPR&D asset, the IPR&D asset is only capitalized if it has an alternative future use other than in a particular research and development project. Otherwise, the cost allocated to acquire an IPR&D asset with no alternative future use is charged to expense at the acquisition date.

Contingent Value Rights

The Company evaluates its contracts to determine if those contracts qualify as derivatives under ASC 815, Derivatives and Hedging ("ASC 815"). For derivative financial instruments that are accounted for as liabilities, the derivative instrument is initially recorded at its fair value and is then re-valued at each reporting date. Any changes in fair value are recorded as other income or expense for each reporting period. Derivative instrument liabilities are classified in the balance sheet as current or non-current based on whether or not net-cash settlement of the derivative instrument is probable within the next 12 months from the balance sheet date. The Company determined that certain contingent payments under the CVR Agreement qualified as derivatives under ASC 815, and as such, were recorded as a liability on the balance sheet. This value is then remeasured for future expected payout as well as the increase in fair value due to the time value of money. These gains or

losses, if any, are recognized in the consolidated statements of operations and comprehensive loss within Other (expense) income, net.

The Company applies a scenario-based method and weighs them based on the possible achievement of certain milestones. The milestone payments are contingent on formal reimbursement decisions by national authorities in key European markets and pegzilarginase approval by the U.S. Food and Drug Administration ("FDA"), among other events. This fair value measurement is based on significant inputs not observable in the market and thus represents a Level 3 measurement as defined in ASC 820, Fair Value Measurement. The key assumptions used include the discount rate, probability of regulatory success, and reimbursement rates from certain government agencies. The estimated value of the CVR consideration is based upon available information and certain assumptions which the Company's management believes are reasonable under the circumstances. The ultimate payout under the CVRs may differ materially from the assumptions used in determining the fair value of the CVR consideration.

Income Taxes

The Company uses the asset and liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are recognized for the expected future tax consequences of temporary differences between the financial statements and the tax bases of assets and liabilities. Additionally, any changes in income tax laws are immediately recognized in the year of enactment.

A valuation allowance is established against the deferred tax assets to reduce their carrying value to an amount that is more likely than not to be realized. The deferred tax assets and liabilities are classified as noncurrent along with the related valuation allowance. Due to a lack of earnings history, the net deferred tax assets have been fully offset by a valuation allowance.

The Company recognizes benefits of uncertain tax positions if it is more likely than not that such positions will be sustained upon examination based solely on the technical merits, as the largest amount of benefits that is more likely than not to be realized upon the ultimate settlement. The Company’s policy is to recognize interest and penalties related to the unrecognized tax benefits as a component of income tax expense, if applicable. As of December 31, 2023 and 2022, the Company had no unrecognized tax benefits and there were no interest or penalties incurred by the Company in the years ended December 31, 2023, 2022, or 2021.

Comprehensive Loss

Comprehensive loss is the change in stockholders’ equity from transactions and other events and circumstances other than those resulting from investments by stockholders and distributions to stockholders. The Company’s other comprehensive income (loss) is currently comprised of changes in unrealized losses and gains on available-for-sale securities and foreign currency translation adjustments reflecting the cumulative effect of changes in exchange rates between the foreign entity’s functional currency and the reporting currency.

Recently Adopted Accounting Pronouncement

The Company early adopted the Financial Accounting Standards Board’s Accounting Standards Update 2020-06, Accounting for Convertible Instruments and Contracts in an Entity’s Own Equity (“ASU 2020-06”), effective as of January 1, 2023 using the modified retrospective method. Among other amendments, ASU 2020-06 eliminates the cash conversion and beneficial conversion feature models in ASC 470-20 that required an issuer of certain convertible debt and preferred stock to separately account for embedded conversion features as a component of equity, as well as changes the accounting for diluted earnings-per-share for convertible instruments and contracts that may be settled in cash or stock. Additionally, ASU 2020-06 requires the if-converted method, which is more dilutive than the treasury stock method, be used for all convertible instruments. The Company applied ASU 2020-06 to all Series A Preferred Stock and Series B Preferred Stock during fiscal year 2023, and, accordingly, the Company did not apply the cash conversion or beneficial conversion feature models in its analysis of the Series A Preferred Stock and Series B Preferred Stock. The adoption of ASU 2020-06 did not have a material impact on the Company's consolidated financial statements.

Recently Issued Accounting Pronouncements

In November 2023, the FASB issued ASU 2023-07, Segment Reporting (Topic 280): Improvements to Reportable Segment Disclosures to update 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 ASU also requires companies with a single reportable segment to provide all disclosures required by Topic 280 – Segment Reporting. This update is effective beginning with the Company's 2024 fiscal year annual reporting period and interim periods beginning thereafter. The Company is currently evaluating the impact that the adoption of this standard will have on its consolidated financial statements.

In December 2023, the FASB issued ASU 2023-09, Income Taxes (Topic 740): Improvements to Income Tax Disclosures. This ASU expands disclosures in an entity's income tax rate reconciliation table and disclosures regarding taxes paid both in the U.S. and foreign jurisdictions. This update is effective beginning with the Company's 2025 fiscal year annual reporting period. This ASU will have no impact on the Company's consolidated financial condition or results of operations. The Company is currently evaluating the impact to its income tax disclosures.

3. Fair Value Measurements

The Company measures and reports certain financial instruments as assets and liabilities at fair value on a recurring basis. The following tables sets forth the fair value of the Company's financial assets and liabilities at fair value on a recurring basis based on the three-tier fair value hierarchy (in thousands):

	December 31, 2023			
	Level 1	Level 2	Level 3	Total
Financial Assets				
Money market funds	$ 150,648	$ —	$ —	$ 150,648
U.S. government treasury securities	32,843	—	—	32,843
U.S. government agency securities	—	16,257	—	16,257
Commercial paper	—	104,141	—	104,141
Corporate bonds	—	33,064	—	33,064
Total financial assets	$ 183,491	$ 153,462	$ —	$ 336,953
Liabilities:				
CVR liability	$ —	$ —	$ 42,700	$ 42,700
Total liabilities	$ —	$ —	$ 42,700	$ 42,700

	December 31, 2022			
	Level 1	Level 2	Level 3	Total
Financial Assets				
Money market funds	$ 15,250	$ —	$ —	$ 15,250
Commercial paper	—	23,641	—	23,641
U.S. government agency securities	—	4,230		4,230
Corporate bonds	—	3,732	—	3,732
Total financial assets	$ 15,250	$ 31,603	$ —	$ 46,853

The Company measures the fair value of money market funds on quoted prices in active markets for identical asset or liabilities. The Level 2 assets include U.S. government agency securities, commercial paper and corporate bonds, and are valued based on quoted prices for similar assets in active markets and inputs other than quoted prices that are derived from observable market data.

The Company evaluates transfers between levels at the end of each reporting period. There were no transfers between Level 1 and Level 2 during the periods presented.

As of December 31, 2022, the Company had no financial liabilities outstanding measured at fair value.

Forward Contract Liability

In connection with the Asset Acquisition, the Company entered into a contract for the issuance of 364,887 shares of Series A Preferred Stock as part of the consideration transferred. This forward contract was classified as a liability because the underlying preferred shares were contingently redeemable. Further, the forward contract liability was considered a Level 2 liability based on observable market data for substantially the full term of the liability and was initially measured at its estimated fair value on the transaction date based on the underlying price per share on an as-converted basis of the Series A PIPE Securities issued in the Series A PIPE. Subsequent remeasurement of the fair value of the forward contract liability through its settlement date was based on the market price of the Company's Common Stock, which represents the redemption value of the Series A Preferred Stock.

The fair value of the forward contract at the transaction date, June 22, 2023, was $106.2 million. The liability was settled with the issuance of the Series A Preferred Stock on July 7, 2023 for $189.7 million. For the year ended December 31, 2023, $83.5 million was recorded as Other (expense) income in the consolidated statements of operations in connection with the change in fair value of the forward contract liability. There was no similar expense for the year ended December 31, 2022 and 2021.

The following table presents changes in the forward contract liability for the periods presented (in millions):

	Forward Contract Liability
Beginning balance as of June 22, 2023	$ 106.2
Change in fair value	83.5
Issuance of Series A Preferred Stock on July 7, 2023	(189.7)
Ending balance as of December 31, 2023	$ —

CVR Liability

In connection with the Asset Acquisition, a non-transferable contingent value right was distributed to the Legacy Stockholders, but was not distributed to holders of shares of Common Stock or Series A Preferred Stock issued to the Investors or former stockholders of Pre-Merger Spyre in connection with the Transactions. Holders of the CVR will be entitled to receive certain cash payments from proceeds received by the Company for a three-year period, if any, related to the disposition or monetization of the Company’s legacy assets for a period of one year following the closing of the Asset Acquisition.

The fair value of the CVR liability was determined using the probability weighted discounted cash flow method to estimate future cash flows associated with the sale of the legacy assets. Analogous to a dividend being declared/approved in one period and paid out in another, the liability was recorded at the date of approval, June 22, 2023, as a Common Stock dividend, returning capital to the Legacy Stockholders. Changes in fair value of the liability will be recognized as a component of Other income (expense) in the consolidated statement of operations and comprehensive loss in each reporting period. The liability value is based on significant inputs not observable in the market such as estimated cash flows, estimated probabilities of regulatory success, and

discount rates, which represent a Level 3 measurement within the fair value hierarchy. The significant inputs used to estimate the fair value of the CVR liability were as follows:

	December 31, 2023
Estimated cash flow dates	2/28/24 - 06/22/26
Estimated probability of success	39% - 100%
Estimated reimbursement rate compared to reimbursement target	81% - 100%
Risk-adjusted discount rates	5.91% - 6.32%

The change in fair value between the issuance of the CVR and December 31, 2023 was a $19.0 million increase, and was primarily driven by changes in the expected timing of achievement of certain milestones, changes in the likelihood of certain milestones related to the approval received from the European Medicines Agency by Immedica Pharma AB ("Immedica"), partially offset by a change in the likelihood of a successful disposition of pegtarviliase and updates to expenses and deductions.

The following table presents changes in the CVR liability for the periods presented (in thousands):

	CVR Liability
Beginning balance as of December 31, 2022	$ —
Fair value at CVR issuance	29,500
Changes in the fair value of the CVR liability since issuance	18,986
Payments	(5,786)
Ending Balance as of December 31, 2023	$ 42,700

4. Cash Equivalents and Marketable Securities

The following tables summarize the estimated fair value of the Company's cash equivalents and marketable securities and the gross unrealized gains and losses (in thousands):

	December 31, 2023			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Cash equivalents:				
Money market funds	$ 150,648	$ —	$ —	$ 150,648
Commercial paper	24,950	5	—	24,955
U.S. government treasury securities	10,965	1	—	10,966
Total cash equivalents	186,563	6	—	186,569
Marketable securities:				
Commercial paper	79,124	62	—	79,186
Corporate bonds	32,984	81	(1)	33,064
U.S. government treasury securities	21,846	31	—	21,877
U.S. government agency securities	16,147	110	—	16,257
Total marketable securities	$ 150,101	$ 284	$ (1)	$ 150,384

	December 31, 2022			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Cash equivalents:				
Money market funds	$ 15,250	$ —	$ —	$ 15,250
Commercial paper	7,021	1	(2)	7,020
U.S. government agency securities	3,736	—	(1)	3,735
Total cash equivalents	$ 26,007	$ 1	$ (3)	$ 26,005
Marketable securities:				
Commercial paper	$ 16,644	$ 2	$ (25)	$ 16,621
Corporate bonds	3,738	—	(6)	3,732
U.S. government agency securities	495	—	—	495
Total marketable securities	$ 20,877	$ 2	$ (31)	$ 20,848

The following table summarizes the available-for-sale securities in an unrealized loss position for which an allowance for credit losses has not been recorded as of December 31, 2023 and 2022, aggregated by major security type and length of time in a continuous unrealized loss position:

	December 31, 2023					
	Less Than 12 Months		12 Months or Longer		Total	
	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses
Commercial paper	$ —	$ —	$ —	$ —	$ —	$ —
Corporate bonds	9,907	(1)	—	—	9,907	(1)
U.S. government treasury securities	4,831	—	—	—	4,831	—
Total marketable securities	$ 14,738	$ (1)	$ —	$ —	$ 14,738	$ (1)

	December 31, 2022					
	Less Than 12 Months		12 Months or Longer		Total	
	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses
Commercial paper	$ 17,699	$ (27)	$ —	$ —	$ 17,699	$ (27)
Corporate bonds	3,732	(6)	—	—	3,732	(6)
U.S. government agency securities	3,735	(1)	—	—	3,735	(1)
Total marketable securities	$ 25,166	$ (34)	$ —	$ —	$ 25,166	$ (34)

The Company evaluated its securities for credit losses and considered the decline in market value to be primarily attributable to current economic and market conditions and not to a credit loss or other factors. Additionally, the Company does not intend to sell the securities in an unrealized loss position and does not expect they will be required to sell the securities before recovery of the unamortized cost basis. As of December 31, 2023 and 2022, an allowance for credit losses had not been recognized. Given the Company's intent and ability to hold such securities until recovery, and the lack of significant change in credit risk of these investments, the Company does not consider these marketable securities to be impaired as of December 31, 2023 and 2022.

There were $0.3 million unrealized gains on marketable securities for the year ended December 31, 2023. There were no realized gains on marketable securities for the year ended December 31, 2023, 2022 and

2021. Interest on marketable securities is included in interest income. Accrued interest receivable on available-for-sale debt securities totaled $0.9 million and $0.1 million as of December 31, 2023 and 2022, respectively, and is excluded from the estimate of credit losses.

The following table summarizes the contractual maturities of the Company's marketable securities at estimated fair value (in thousands):

	December 31,	
	2023	2022
Due in one year or less	$ 115,784	$ 20,848
Due in 1 - 2 years	34,600	—
Total marketable securities	$ 150,384	$ 20,848

The Company may sell investments at any time for use in current operations even if they have not yet reached maturity. As a result, the Company classifies marketable securities, including securities with maturities beyond twelve months as current assets.

5. Property and Equipment, Net

Property and equipment, net consist of the following (in thousands):

	December 31,	
	2023	2022
Laboratory equipment	$ —	$ 2,257
Furniture and office equipment	—	520
Computer equipment	—	73
Software	—	121
Leasehold improvements	—	4,393
Property and equipment, gross	—	7,364
Less: Accumulated depreciation and amortization	—	(4,144)
Property and equipment, net	$ —	$ 3,220

Depreciation and amortization expense for the years ended December 31, 2023, 2022, and 2021 was $0.7 million, $1.4 million, and $1.4 million, respectively. All of the Company’s long-lived assets were located in the United States.

Sale of Assets

On April 12, 2023, based on the review of the inconclusive interim results from the Company's Phase 1/2 clinical trial of pegtarviliase for the treatment of classical homocystinuria and other business considerations, the Company announced that it had initiated a process to explore strategic alternatives to maximize stockholder value and engaged an independent exclusive financial advisor to support this process. As a result, the Company implemented a restructuring plan resulting in an approximate 83% reduction of the Company’s existing headcount by June 30, 2023.

During the second quarter of 2023, the Company sold various lab equipment, consumables, and furniture and fixtures for total consideration of $0.5 million. After recording the disposal of all the Company's property and equipment net of proceeds, the Company recorded a $0.7 million and $0.2 million loss on disposal of long lived assets which is included in Research and development and General and administrative expenses, respectively.

6. Accrued and Other Current Liabilities

Accrued and other current liabilities consist of the following (in thousands):

	December 31,	
	2023	2022
Accrued compensation	$ 4,054	$ 4,589
Accrued contracted research and development costs	7,092	6,972
Accrued professional and consulting fees	1,474	946
Other	488	330
Total accrued and other current liabilities	$ 13,108	$ 12,837

7. Related Party Transactions

Paragon and Parapyre Holding LLC ("Parapyre") each beneficially own less than 5% of the Company's capital stock through their respective holdings of the Company's common stock. Fairmount Funds Management LLC ("Fairmount") beneficially owns more than 5% of the Company's capital stock on an as-converted basis, has two seats on the Board and beneficially owns more than 5% of Paragon, which is a joint venture between Fairmount and Fair Journey Biologics. Fairmount appointed Paragon's board of directors and has the contractual right to approve the appointment of any executive officers. Parapyre is an entity formed by Paragon as a vehicle to hold equity in Spyre in order to share profits with certain employees of Paragon.

In connection with the Asset Acquisition, the Company assumed the rights and obligations of Pre-Merger Spyre under the Paragon Agreement. Under the Paragon Agreement, Spyre is obligated to compensate Paragon for its services performed under each research program based on the actual costs incurred with mark-up costs pursuant to the terms of the Paragon Agreement. As of the date of the Asset Acquisition, Pre-Merger Spyre had incurred total expenses of $19.0 million under the Paragon Agreement since inception, which included the $3.0 million research initiation fee and $16.0 million of reimbursable expenses under the Paragon Agreement for historical costs owed to Paragon. As of the acquisition date, $19.0 million was unpaid and was assumed by the Company through the Asset Acquisition.

For the year ended December 31, 2023, the Company recognized expenses related to services provided by Paragon subsequent to the Asset Acquisition totaling $48.5 million, which included $11.4 million of stock-based compensation expense, and were recorded as Research and development expenses in the consolidated statements of operations. As of December 31, 2023, $16.6 million was unpaid and was included in Related party accounts payable and other current liabilities on the Company's consolidated balance sheets.

For the year ended December 31, 2023, the Company made payments totaling $39.5 million to Paragon.

On July 12, 2023 and December 14, 2023, the Company exercised the Option available under the Paragon Agreement with respect to the SPY001 and SPY002 research programs, respectively, and expects to enter into the SPY001 License Agreement and the SPY002 License Agreement.

Following the execution of each of the SPY001 License Agreement and SPY002 License Agreement, the Company will be obligated to pay Paragon up to $22.0 million upon the achievement of specific development, regulatory and clinical milestones for the first product under each agreement, respectively, that achieves such specified milestones. Upon execution of each of the SPY001 License Agreement and the SPY002 License Agreement, we expect to pay Paragon a $1.5 million fee for nomination of a development candidate, as applicable, and the Company expects to be obligated to make a further milestone payment of $2.5 million upon the first dosing of a human patient in a Phase 1 trial.

The following is the summary of expenses related to the Paragon Agreement recognized within research and development expenses, which were ultimately settled in cash (in millions):

	December 31,		
	2023	2022	2021
Reimbursable costs under the Paragon Agreement	$ 37.1	$ —	$ —

Parapyre Option Obligation

As part of the Paragon Agreement, the Company is obligated to issue Parapyre a stock option grant on the last business day of 2023 and 2024 (the "Parapyre Option Obligation"). See Note 15 for additional information.

The following is the summary of Related party accounts payable and other current liabilities (in millions):

	December 31, 2023	December 31, 2022
Reimbursable costs under the Paragon Agreement	$ 16.6	$ —
Related party accounts payable and other current liabilities	$ 16.6	$ —

December 2023 PIPE

The December 2023 Investors included Fairmount, a related party. Fairmount's participation in the December 2023 PIPE was approved by the Company's board of directors. Fairmount's investment accounted for $10.0 million of the $180.0 million gross proceeds raised in the December 2023 PIPE.

Mark McKenna Option Grant

On February 1, 2024, the Board appointed Mark McKenna as a Class I director. Mr. McKenna and the Company are parties to a consulting agreement, pursuant to which Mr. McKenna agreed to continue to provide consulting services as an independent contractor to the Company, with an effective date of August 1, 2023 (the “Vesting Commencement Date”). As compensation for Mr. McKenna’s consulting services, on November 22, 2023, he was granted non-qualified stock options to purchase 477,000 shares of the Company’s common stock under the Company's equity incentive plan with an exercise price of $10.39 per share, which vest as to 25% on the one year anniversary of the Vesting Commencement Date and thereafter vest and become exercisable in 48th equal monthly installments, subject to Mr. McKenna’s continued service to the Company through each applicable vesting date. For the twelve months ended December 31, 2023, the Company recognized $0.1 million in stock-based compensation expense related to Mr. McKenna's consulting agreement. There was no such expense for the twelve months ended December 31, 2022 and 2021.

8. Asset Acquisition

On June 22, 2023, the Company acquired Pre-Merger Spyre pursuant to the Acquisition Agreement, by and among the Company, Aspen Merger Sub I, Inc., a Delaware corporation and a wholly owned subsidiary of the Company (“First Merger Sub”), Sequoia Merger Sub II, LLC, a Delaware limited liability company and a wholly owned subsidiary of the Company (“Second Merger Sub”), and Pre-Merger Spyre. Pursuant to the Acquisition Agreement, First Merger Sub merged with and into Pre-Merger Spyre, pursuant to which Pre-Merger Spyre was the surviving corporation and became the Company's wholly owned subsidiary (the “First Merger”). Immediately following the First Merger, Pre-Merger Spyre merged with and into Second Merger Sub, pursuant to which Second Merger Sub became the surviving entity. Pre-Merger Spyre was a pre-clinical stage biotechnology company that was incorporated on April 28, 2023 under the direction of Peter Harwin, a Managing Member of Fairmount, for the purpose of holding rights to certain intellectual property being developed by Paragon. Fairmount is a founder of Paragon.

With respect to the Asset Acquisition, the Company determined that Aeglea was the acquirer for accounting purposes under ASC 805. The primary factors considered were a) the relative voting rights in the combined entity not resulting in a change of control, b) legacy members of the Company's Board of Directors maintained control of the Board of Directors, and c) the only change in the composition of senior management was the appointment of a new Chief Operating Officer. Next, the Company considered whether the Asset Acquisition should be defined as a business under ASC 805. ASC 805-10-55-5A through 55-5C describe a screen test to determine whether an acquired set of assets and activities is not a business. We determined that substantially all (greater than 90%) of the fair value of the assets acquired were concentrated in a single asset, Spyre’s Option to license intellectual property rights related to SPY001, SPY002, SPY003 and SPY004

pursuant to the Paragon Agreement. Accordingly, the Company treated the Asset Acquisition as an asset acquisition for accounting purposes. Even if the transaction would have failed the screen test, Pre-Merger Spyre lacked the financial resources to have inputs, processes, and outputs to constitute a business under ASC 805.

The Company completed the Asset Acquisition of Pre-Merger Spyre, in accordance with the terms of the Acquisition Agreement. Under the terms of the Acquisition Agreement, the Company issued 517,809 shares of Common Stock and 364,887 shares of Series A Preferred Stock to former Pre-Merger Spyre security holders. In addition, outstanding and unexercised stock options to purchase 2,734 shares of common stock were assumed from the Amended and Restated Spyre 2023 Equity Incentive Plan.

At the acquisition date, the Company recorded forward contracts to represent the obligation to issue shares of the Company's Common Stock and shares of Series A Preferred Stock. The forward contract related to the Common Stock was recorded as Additional paid-in capital as the instrument is indexed to the Company's Common Stock. The forward contract related to the Series A Preferred Stock was recorded as a liability, as the underlying stock has a cash redemption feature. On July 7, 2023, both the shares of Common Stock and Series A Preferred Stock were issued and the forward contract liability associated with the Series A Preferred Stock was settled accordingly.

The Company concluded that the arrangement meets the definition of an asset acquisition rather than a business combination, as substantially all of the fair value of the gross assets acquired is concentrated in a single identifiable asset, the Option to exclusively license IPR&D. The Company determined that the Option to license IPR&D was a single asset as the Company's strategy relies on developing the entire portfolio of individual treatments to create combination treatments that simultaneously address different mechanisms of irritable bowel disease with a single treatment. The Company also determined that the pipeline candidates within the portfolio are similar in nature and risk profile. In addition, the Company did not obtain any substantive processes, assembled workforce, or employees capable of producing outputs in connection with the Asset Acquisition.

The Company determined that the cost to acquire the asset was $113.2 million which was recorded as acquired IPR&D. The fair value of the consideration issued consisted of the 364,887 shares of Series A Preferred Stock (14,595,480 shares of Common Stock on an as-converted basis) and 517,809 shares of Common Stock, valued at $291.08 per share and $7.277 per share, respectively.

The Asset Acquisition Costs are shown on the following table (in millions):

	June 22, 2023
Consideration transferred in Series A Preferred Stock and Common Stock	$ 110.0
Transaction costs incurred by the Company	3.2
Total cost to acquire asset	$ 113.2

The allocation of the purchase price to net assets acquired is as a follows:

	June 22, 2023
Acquired in-process research and development	$ 130.2
Cash acquired	3.0
Assumed liabilities	(20.0)
Total cost to acquire asset	$ 113.2

9. Paragon Agreement

In May 2023, Pre-Merger Spyre entered into the Paragon Agreement with Paragon and Parapyre. Pursuant to the Paragon Agreement, the Option provided for the right to acquire the intellectual property rights related to four research programs from Paragon in accordance with a license agreement to be entered into following each exercise of the Option. Under the Paragon Agreement, the terms of such license agreement

would be consistent with the economics and other terms set out in the Paragon Agreement and, in the event of failure to reach an agreement on the definitive terms, the matter would be resolved via arbitration. In consideration for the Option granted under the Paragon Agreement, Pre-Merger Spyre was obligated to pay Paragon an upfront cash amount of $3.0 million in research initiation fees. In addition, Pre-Merger Spyre was obligated to compensate Paragon on a quarterly basis for its services performed under each research program based on the actual costs incurred with mark-up costs pursuant to the terms of the Paragon Agreement. As of the date of the Asset Acquisition, Pre-Merger Spyre had incurred total expenses of $19.0 million under the Paragon Agreement since inception, which included the $3.0 million research initiation fee and $16.0 million of historical reimbursable expenses owed to Paragon. As of June 22, 2023, $19.0 million was unpaid and was assumed by the Company through the Asset Acquisition. Furthermore, the Paragon Agreement provided for an annual equity grant of options to purchase 1% of the then outstanding shares of Spyre's common stock, on a fully diluted basis, on the last business day of each calendar year, during the term of the Paragon Agreement, at the fair market value determined by the board of directors of Spyre.

As a result of the Asset Acquisition, the Company assumed the rights and obligations of Pre-Merger Spyre under the Paragon Agreement, including the Parapyre Option Obligation. Pursuant to the Paragon Agreement, on a research program-by-research program basis following the finalization of the research plan for each respective research program, the Company is required to pay Paragon a nonrefundable fee in cash of $0.8 million. For the year ended December 31, 2023, the Company incurred $48.5 million, in costs reimbursable to Paragon, which were recorded as Research and development expenses in the consolidated statements of operations.

For the year ended December 31, 2023, the Company made payments totaling $39.5 million to Paragon.

On July 12, 2023 and December 14, 2023, the Company exercised the Option available under the Paragon Agreement with respect to the SPY001 and SPY002 research programs, respectively, and expects to enter into the SPY001 License Agreement and the SPY002 License Agreement. Our Option available under the Paragon Agreement with respect to the SPY003 and SPY004 programs remains unexercised.

Following the execution of each of the SPY001 License Agreement and SPY002 License Agreement, the Company will be obligated to pay Paragon up to $22.0 million upon the achievement of specific development, regulatory and clinical milestones for the first product under each agreement, respectively, that achieves such specified milestones. Upon execution of each of the SPY001 License Agreement and the SPY002 License Agreement, the Company expects to pay Paragon a $1.5 million fee for nomination of a development candidate, as applicable, and the Company expects to be obligated to make a further milestone payment of $2.5 million upon the first dosing of a human patient in a Phase 1 trial. Subject to the execution of the Option with respect to the SPY003 or SPY004 research programs, the Company expects to be obligated to make similar payments upon and following the execution of license agreements with respect to these research programs, respectively.

10. Leases

Prior to the Company's restructuring, as described in Note 17, the Company leased certain office space, laboratory facilities, and equipment. These leases required monthly lease payments that were subject to annual increases throughout the lease term. Certain of these leases also included renewal options at the election of the Company to renew or extend the lease for an additional three to five years. These optional periods were not considered in the determination of the right-of-use assets or lease liabilities associated with these leases as the Company did not consider it reasonably certain it would exercise the options. The Company performed evaluations of its contracts and determined it has both operating and finance leases. Variable lease expense for these leases primarily consisted of common area maintenance and other operating costs.

In April 2019, the Company entered into a lease agreement (the "Las Cimas Lease") for its corporate headquarters and laboratory space located in Austin, Texas. The Las Cimas Lease included approximately 30,000 square feet and commenced on April 30, 2019, with an expiration on April 30, 2028. The Company posted a customary letter of credit in the amount of $1.5 million as security, which is subject to automatic reductions per the terms of the Las Cimas Lease. A tenant allowance of up to $1.0 million was provided by the lessor and fully reimbursed to the Company.

In August 2023, the Company terminated its building lease in Austin, Texas. The negotiated termination agreement obligated the Company to pay the lessor a $2.0 million termination fee in exchange for releasing the Company of all further obligations under the lease including terminating the associated letter of credit.

The following table summarizes the Company's recognition of its operating and finance leases (in thousands):

	Classification	December 31, 2023	December 31, 2022
Assets			
Operating	Operating lease right-of-use assets	$ —	$ 3,430
Finance	Other non-current assets	—	597
Total leased assets		—	4,027
Leases			
Current			
Operating	Operating lease liabilities	—	625
Finance	Accrued and other current liabilities	—	16
Non-current			
Operating	Non-current operating lease liabilities	—	4,004
Total lease liabilities		$ —	$ 4,645

The following table summarizes the weighted-average remaining lease term and discount rates for the Company's operating and finance leases:

	December 31, 2023	December 31, 2022
Lease term (years)		
Operating leases	0.0	5.3
Finance leases	0.0	0.6
Discount rate		
Operating leases	— %	10.6 %
Finance leases	— %	10.2 %

The following table summarizes the lease costs pertaining to the Company's operating leases (in thousands):

	Year Ended December 31, 2023	2022	2021
Operating lease cost	$ 455	$ 910	$ 991
Variable lease cost	471	472	519
Total lease cost	$ 926	$ 1,382	$ 1,510

Cash paid for amounts included in the measurement of operating lease liabilities during the years ended December 31, 2023 and 2022 was $0.5 million and $0.9 million, respectively, and was included within net cash used in operating activities in the cash flows.

As of December 31, 2023, the Company had no operating or finance lease obligations.

11. Convertible Preferred Stock and Stockholders' Equity

The Company is authorized to issue 410,000,000 shares of capital stock of which 400,000,000 shares are designated as Common Stock and 10,000,000 shares are designated as preferred stock, all with a par value of $0.0001 per share. Each holder of Common Stock is entitled to one vote for each share of Common Stock held. The Common Stock is not entitled to preemptive rights, and is not subject to conversion, redemption or sinking fund provisions. Subject to preferences that may apply to any shares of preferred stock outstanding at the time, the holders of Common Stock are entitled to receive dividends out of funds legally available if the board of directors, in its discretion, determines to issue dividends and then only at the times and in the amounts that the board of directors may determine.

As of December 31, 2023 and 2022, no Common Stock dividends had been declared by the board of directors. As of December 31, 2023 there were 437,037 shares of Series A preferred stock and 150,000 shares of Series B preferred stock outstanding. There were no shares of Series A preferred stock or shares of Series B preferred stock outstanding as of December 31, 2022.

Registered Direct Offering

In May 2022, the Company issued and sold 430,107 shares of Common Stock at an offering price of $40.00 per share and pre-funded warrants to purchase up to 694,892 shares of Common Stock at an offering price of $39.9975 per warrant (representing the price per share of Common Stock sold in the offering minus the $0.0025 exercise price per warrant) in a registered direct offering pursuant to a shelf registration statement on Form S-3. The net proceeds to the Company from this offering were approximately $42.9 million, after deducting placement agent fees and offering costs of $2.1 million.

June 2023 PIPE

In June 2023, in connection with the Asset Acquisition, the Company issued and sold 721,452 shares of Series A Preferred Stock at approximately $291.08 per share through a private placement to a group of accredited investors. The net proceeds from this offering were approximately $197.3 million, after deducting placement agent fees and offering costs of $12.7 million.

December 2023 PIPE

In December 2023, the Company issued and sold 6,000,000 shares of Common Stock at an offering price of $15.00 per share and 150,000 shares of Series B Preferred Stock at $600 per share through a private placement to a group of accredited investors. The net proceeds from this offering were approximately $169.1 million, after deducting placement agent fees and offering costs of $10.9 million.

Parapyre Warrants

The Company settled its 2023 obligations under the Parapyre Option Obligation by issuing Parapyre 684,407 warrants to purchase the Company's common stock, less the $21.52 per share exercise price of each warrant. As of December 31, 2023, none of the warrants issued under the Parapyre Option Obligation have been exercised. See Note 15 for additional information on the Parapyre Option Obligation.

Pre-Funded Warrants

In May 2022, the Company issued pre-funded warrants to purchase shares of Common Stock in underwritten public offerings at the offering price of the Common Stock, less the $0.0025 per share exercise price of each warrant. The warrants were recorded as a component of stockholders' equity within additional paid-in capital and have no expiration date. Per the terms of the warrant agreements, the outstanding warrants to purchase shares of Common Stock may not be exercised if the holder's ownership of the Common Stock would exceed 4.99% ("Maximum Ownership Percentage") or 9.99% for certain holders. By written notice to the Company, each holder may increase or decrease the Maximum Ownership Percentage to any other percentage (not in excess of 19.99% for the majority of such warrants). The revised Maximum Ownership Percentage would be effective 61 days after the notice is received by the Company.

As of December 31, 2023, the following pre-funded warrants to purchase Common Stock were issued and outstanding:

Issue Date	Expiration Date	Exercise Price	Number of Warrants Outstanding
May 2022	None	$ 0.0025	250,000
Total pre-funded warrants			250,000

Series A Non-Voting Convertible Preferred Stock

On June 22, 2023, the Company filed a Certificate of Designation of Preferences, Rights and Limitations of the Series A Preferred Stock with the Secretary of State of the State of Delaware (the "Certificate of Designation") in connection with the Asset Acquisition and the PIPE.

Pursuant to the Certificate of Designation, holders of Series A Preferred Stock are entitled to receive dividends on shares of Series A Preferred Stock equal to, on an as-if-converted-to-Common Stock basis, and in the same form as, dividends actually paid on shares of Common Stock. Except as provided in the Certificate of Designation or as otherwise required by law, the Series A Preferred Stock does not have voting rights. However, as long as any shares of Series A Preferred Stock are outstanding, the Company will not, without the affirmative vote of the holders of a majority of the then outstanding shares of the Series A Preferred Stock: (a) alter or change adversely the powers, preferences or rights given to the Series A Preferred Stock, or alter or amend the Certificate of Designation, amend or repeal any provision of, or add any provision to, the Company's Certificate of Incorporation or its Bylaws, or file any articles of amendment, certificate of designations, preferences, limitations and relative rights of any series of Preferred Stock, if such action would adversely alter or change the preferences, rights, privileges or powers of, or restrictions provided for the benefit of the Series A Preferred Stock, regardless of whether any of the foregoing actions will be by means of amendment to the Certificate of Incorporation or by merger, consolidation, recapitalization, reclassification, conversion or otherwise, (b) issue further shares of Series A Preferred Stock or increase or decrease (other than by conversion) the number of authorized shares of Series A Preferred Stock, (c) prior to the stockholder approval of the conversion of the Series A Preferred Stock into shares of Common Stock in accordance with Nasdaq Stock Market Rules (the "Conversion Proposal") or at any time while at least 30% of the originally issued Series A Preferred Stock remains issued and outstanding, consummate (x) any Fundamental Transaction (as defined in the Certificate of Designation) or (y) any merger or consolidation of the Company with or into another entity or any stock sale to, or other business combination in which our stockholders immediately before such transaction do not hold at least a majority of our capital stock immediately after such transaction or (d) enter into any agreement with respect to any of the foregoing. The Series A Preferred Stock does not have a preference upon any liquidation, dissolution or winding-up of the Company.

The Company held a stockholders' meeting to submit the following matters to its stockholders for their consideration: (i) the approval of the Conversion Proposal, and (ii) if deemed necessary or appropriate by the Company or as otherwise required by law or contract, the approval of an amendment to the Certificate of Incorporation to authorize sufficient shares of Common Stock for the conversion of the Series A Preferred Stock issued pursuant to the Acquisition Agreement. In connection with these matters, the Company filed with the SEC a definitive proxy statement and other relevant materials.

Following stockholder approval of the Conversion Proposal, each share of Series A Preferred Stock automatically converted into 40 shares of Common Stock, subject to certain limitations, including that a holder of Series A Preferred Stock is prohibited from converting shares of Series A Preferred Stock into shares of Common Stock if, as a result of such conversion, such holder, together with its affiliates, would beneficially own more than a specified percentage (established by the holder between 0.0% and 20.0%) of the total number of shares of Common Stock issued and outstanding immediately after giving effect to such conversion.

On June 26, 2023, the Company completed a private placement of 721,452 shares of Series A PIPE Securities in exchange for gross proceeds of $210.0 million, or net proceeds of $197.3 million, after deducting placement agent and other offering costs.

On July 7, 2023, the Company issued 364,887 shares of Series A Preferred Stock as part of its consideration transferred in connection with the Asset Acquisition that closed on June 22, 2023 which settled the related forward contract liability. For additional information, see Note 3.

On November 21, 2023, the Company's stockholders approved the Conversion Proposal, among other matters, at a special meeting of stockholders. As a result of the approval of the Conversion Proposal, all conditions that could have required cash redemption of the Series A Preferred Stock were satisfied. Since the Series A Preferred Stock is no longer redeemable, the associated balances of the Series A Preferred Stock were reclassified from mezzanine equity to permanent equity during the fourth quarter of 2023. In addition, 649,302 shares of Series A Preferred Stock automatically converted to 25,972,080 shares of Common Stock; 437,037 shares of Series A Preferred Stock did not automatically convert and remain outstanding as of December 31, 2023 due to beneficial ownership limitations. This conversion was recorded as a reclassification between Series A Preferred Stock and Common Stock based on the historical per-share contributed capital amount, inclusive of any forward-contract valuation adjustments, of the Series A Preferred Stock.

Series B Non-Voting Convertible Preferred Stock

On December 8, 2023, the Company filed a Certificate of Designation of Preferences, Rights and Limitations of Series B Non-Voting Convertible Preferred Stock with the Secretary of State of the State of Delaware (the “Series B Certificate of Designation”) in connection with the December 2023 PIPE.

Pursuant to the Series B Certificate of Designation, holders of Series B Preferred Stock are entitled to receive dividends on shares of Series B Preferred Stock equal to, on an as-if-converted-to-Common Stock basis, and in the same form as, dividends actually paid on shares of Common Stock. Except as provided in the Series B Certificate of Designation or as otherwise required by law, the Series B Preferred Stock does not have voting rights. However, as long as any shares of Series B Preferred Stock are outstanding, the Company will not, without the affirmative vote of the holders of a majority of the then outstanding shares of the Series B Preferred Stock, alter or change adversely the powers, preferences or rights given to the Series B Preferred Stock, or alter or amend the Series B Certificate of Designation, amend or repeal any provision of, or add any provision to, the Company’s Certificate of Incorporation or its Bylaws, or file any articles of amendment, certificate of designations, preferences, limitations and relative rights of any series of Preferred Stock, if such action would adversely alter or change the preferences, rights, privileges or powers of, or restrictions provided for the benefit of the Series B Preferred Stock, regardless of whether any of the foregoing actions will be by means of amendment to the Certificate of Incorporation or by merger, consolidation, recapitalization, reclassification, conversion or otherwise. The Series B Preferred Stock does not have a preference upon any liquidation, dissolution or winding-up of the Company.

The Company has agreed to use its best efforts to obtain stockholder approval of the conversion of all issued and outstanding Series B Preferred Stock into shares of Common Stock in accordance with the Nasdaq Stock Market Rules (the "Series B Conversion Proposal") at its 2024 annual meeting of stockholders, which the Company agreed to hold no later than May 15, 2024. The Series B Preferred Stock is recorded outside of stockholders’ equity because, if conversion to Common Stock is not approved by the stockholders, the Series B Preferred Stock will be redeemable at the option of the holders for cash equal to the closing price of the Common Stock per share of Common Stock underlying the Series B Preferred Stock, on the last trading day prior to the holder’s redemption request. As of December 31, 2023, the redemption value of the Company's outstanding Series B Preferred Stock was $129.1 million based on the closing stock price of the Company's Common Stock on December 31, 2023 of $21.52 per share. The Company has determined that the Series B Preferred Stock did not contain any embedded derivatives and therefore the conversion and redemption features did not require bifurcation.

Following stockholder approval of the Series B Conversion Proposal, each share of Series B Preferred Stock will automatically convert into 40 shares of the Common Stock, subject to certain limitations, including that a holder of Series B Preferred Stock is prohibited from converting shares of Series B Preferred Stock into shares of Common Stock if, as a result of such conversion, such holder, together with its affiliates, would beneficially own more than a specified percentage (established by the holder between 0% and 19.99%) of the total number of shares of Common Stock issued and outstanding immediately after giving effect to such conversion.

On December 11, 2023, as part of the December 2023 PIPE, the Company completed a private placement of 150,000 shares of Series B Preferred Stock in exchange for gross proceeds of $90.0 million.

12. Strategic License Agreements

Immedica Pharma AB License and Development Agreement

On March 21, 2021, the Company entered into an exclusive license and supply agreement with Immedica Pharma AB ("Immedica"). By entering into this agreement, the Company agreed to provide Immedica the following goods and services:

i. Deliver an exclusive, sublicensable, license and know-how (the "License") to develop and commercialize pegzilarginase (the "Product") in the territory comprising the members states of the European Economic Area, United Kingdom, Switzerland, Andorra, Monaco, San Marino, Vatican City, Turkey, Saudi Arabia, United Arab Emirates, Qatar, Kuwait, Bahrain, and Oman (the "Territory");

ii. Complete the global pivotal PEACE (Pegzilarginase Effect on Arginase 1 Deficiency Clinical Endpoints) Phase 3 trial ("PEACE Trial") and related Biologics License Application ("BLA") package to file with the United States Food and Drug Administration ("FDA"), which will be leveraged by Immedica in obtaining the necessary regulatory approvals in the Territory; and

iii. Perform a Pediatric Investigation Plan trial ("PIP Trial") in order for Immedica to be able to receive certain regulatory approvals within the Territory.

In addition, the Company and Immedica formed a Joint Steering Committee ("JSC") to provide oversight to the activities performed under the agreement; however, the substance of the Company's participation in the JSC does not represent an additional promised service, but rather, a right of the Company to protect its own interests in the arrangement.

Further, the Company agreed to supply to Immedica, and Immedica agreed to purchase from the Company, substantially all commercial requirements of the Product. The terms of the agreement do not provide for either (i) an option to Immedica to purchase the Product from the Company at a discount from the standalone selling price or (ii) minimum purchase quantities. Finally, Immedica will bear (i) all costs and expenses for any development or commercialization of the Product in the Territory subject to the License exclusive of the Company's promised goods and services summarized above and (ii) all costs and fees associated with applying for regulatory approval of the Product in the Territory. In July 2021, the Company modified the agreement with Immedica to provide certain additional services in relation to the PEACE Phase 3 Trial and BLA package performance obligation in exchange for the reimbursement of up to $3.0 million of the actual costs incurred in relation to such incremental services.

The Company received a non-refundable payment of $21.5 million and Immedica agreed to provide payment of 50% of the Company's costs incurred in performing the PIP Trial up to a maximum of $1.8 million. In addition, the Company has the ability to receive additional payments under the agreement of up to approximately $120.8 million in regulatory and commercial milestone payments, assuming an exchange rate of $1.07 to €1.00. The Company is also entitled to receive royalties in the mid-20 percent range on net sales of the Product in the Territory.

The Company concluded that Immedica meets the definition to be accounted for as a customer because the Company is delivering intellectual property and other services within the Company's normal course of business, in which the parties are not jointly sharing the risks and rewards. Therefore, the Company concluded that the promises summarized above represent transactions with a customer within the scope of ASC 606. The Company determined that the following promises represent distinct promised services, and therefore, performance obligations: (i) the License, (ii) the PEACE Trial and BLA package, and (iii) the PIP Trial.

Specifically, in making these determinations, the Company considered the following factors:

- As of inception of the agreement, the Company had completed the Phase 1/2 clinical trial related to the Product and were conducting the ongoing PEACE Trial. Accordingly, the

Company is not promising, nor expecting, to perform additional research and development activities pursuant to the agreement that would either significantly modify, customize or be considered highly interdependent or interrelated with pegzilarginase.

- The License represents functional intellectual property given the functionality of the License is not expected to change substantially as a result of the company's ongoing activities.
- The services necessary to complete the PEACE Trial, BLA package and PIP Trial could be performed by other parties.

Given that Immedica was not obligated to purchase any minimum amount or quantities of the Product, the supply of the Product for commercial use to Immedica was determined to be an option for Immedica, rather than a performance obligation of the Company at contract inception and will be accounted for if and when exercised. The Company also determined that Immedica's option to purchase the Product does not create a material right as the expected pricing is not at a discount.

The Company determined that the upfront fixed payment amount of $21.5 million must be included in the transaction price. Additionally, the Company determined at inception of the arrangement that 50% of the estimated costs to be incurred in relation to the PIP Trial exceeded $1.8 million and included the full reimbursement amount of $1.8 million in the transaction price. Upon subsequent re-evaluation due to changing facts and circumstances, the Company determined the estimated costs are now less than the maximum allowable reimbursement and a portion of the variable consideration was constrained, which did not materially impact the revenue recognized to date. Additionally, upon the modification of the agreement in July 2021, the Company determined that the estimated costs to perform the additional services related to the PEACE Trial and BLA package exceeds the maximum allowable reimbursement of $3.0 million. Therefore, the Company included an estimated total of $3.6 million that will be due in relation to the PIP Trial, PEACE Trial, and BLA package in the transaction price and it is probable that a significant reversal will not occur in the future. In total, the modified transaction price was determined to be $25.1 million.

The Company has allocated $9.6 million and $3.5 million of the modified transaction price to the PEACE Trial and BLA package and PIP Trial performance obligations, respectively, based on the stand-alone selling prices ("SSP"), which was based on the estimated costs that a third-party would charge in performing such services on a stand-alone basis. The SSP for the License was established at inception of the arrangement using a residual value approach due to the uniqueness of and lack of observable data related to the License, and without a specific analog from which to make reliable estimates, resulting in an allocation of $12.0 million.

The potential regulatory milestone payments that the Company is eligible to receive were excluded from the transaction price, as the milestone amounts were fully constrained based on the probability of achievement, since the milestones relate to successful achievement of certain regulatory approvals, which might not be achieved. The Company determined that the royalties and commercial milestone payments relate predominantly to the license of intellectual property and are therefore excluded from the transaction price under the sales- or usage-based royalty exception of ASC 606. The Company will reevaluate the transaction price, including all constrained amounts, at the end of each reporting period and as uncertain events are resolved or other changes in circumstances occur, the Company will adjust its estimate of the transaction price as necessary. The Company will recognize the royalties and commercial milestone payments as revenue when the associated sales occur, and relevant sales-based thresholds are met. The Company assessed the arrangement with Immedica and concluded that a significant financing component does not exist.

The Company recognized revenue allocated to the License performance obligation at a point in time and upon transfer of the License. The Company completed the transfer of the know-how necessary for Immedica to benefit from the License in June 2021 and recognized $12.0 million of revenue at that time. The development fee allocated to the PEACE Trial, BLA package and PIP Trial performance obligations will be recognized over time using an input method of costs incurred related to the performance obligations.

For the years ended December 31, 2023 and 2022, the Company recognized revenue of $0.9 million and $2.3 million, respectively, related to the PEACE Trial and BLA package performance obligation using a cost to cost model. The Company recognized revenue of $6.7 million related to the PEACE Trial and BLA package performance obligation using a cost to cost model and $12.0 million related to the transfer of the License for the year ended December 31, 2021. As of December 31, 2022, the Company recorded deferred revenue of $2.7

million associated with the license and supply agreement with Immedica, of which $0.5 million was classified as current.

On July 27, 2023, the Company announced that it had entered into an agreement to sell the global rights to pegzilarginase to Immedica for $15.0 million in upfront cash proceeds and up to $100.0 million in contingent milestone payments. The sale of pegzilarginase to Immedica superseded and terminated the previous license agreement between the Company and Immedica. On July 27, 2023, the carrying value of the asset was zero as it was internally developed. Accordingly, the Company recognized a $16.4 million gain within Gain on Sale of in-process research and development, which is comprised of $15.0 million in upfront cash proceeds and the reimbursement of $1.8 million in pre-paid manufacturing costs that was contingent upon a favorable opinion being received by the CHMP, net of transaction costs and the derecognition of pegzilarginase related nonfinancial assets and liabilities totaling $0.4 million.

The milestone payments are contingent on formal reimbursement decisions by national authorities in key European markets and pegzilarginase approval by the FDA, among other events. The upfront payment and contingent milestone payments if paid, net of expenses and adjustments, will reduce the CVR liability and will be distributed to CVR holders pursuant to the CVR Agreement resulting from the Asset Acquisition.

Contract Balances from Customer Contract

The timing of revenue recognition, billings and cash collections results in contract assets and contract liabilities on the balance sheets. The Company recognizes license and development receivables based on billed services, which are derecognized upon reimbursement. When consideration is received, or such consideration is unconditionally due, from a customer prior to transferring goods or services to the customer under the terms of a contract, a contract liability is recorded. Contract liabilities are recognized as revenue after control of the goods or services is transferred to the customer and all revenue recognition criteria have been met.

The following table presents changes in the Company's contract liabilities for the periods presented (in thousands):

Year Ended December 31, 2022	December 31, 2022	Additions	Deductions	December 31, 2023
Contract liabilities:				
Deferred revenue	$ 2,696	$ 575	$ (3,271)	$ —

The Company had no contract assets during the years ended December 31, 2023 and 2022.

13. Sale of Pegzilarginase to Immedica

On July 27, 2023, the Company announced that it had entered into an agreement to sell the global rights to pegzilarginase to Immedica for $15.0 million in upfront cash proceeds and up to $100.0 million in contingent milestone payments. The sale of pegzilarginase to Immedica superseded and terminated the previous license agreement between the Company and Immedica. On July 27, 2023, the carrying value of the asset was zero as it was internally developed. Accordingly the Company recognized a $16.4 million gain within Gain on sale of in-process research and development, which is comprised of $15.0 million in upfront cash proceeds and the reimbursement of $1.8 million in pre-paid manufacturing costs that was contingent upon a favorable opinion being received by the Committee for Medicinal Products for Human Use, net of transaction costs and the derecognition of pegzilarginase related nonfinancial assets and liabilities totaling $0.4 million.

The milestone payments are contingent on formal reimbursement decisions by national authorities in key European markets and pegzilarginase approval by the FDA, among other events. Accordingly, the Company will recognize any future milestone payments once the contingency is resolved and payment is contractually required. The upfront payment and contingent milestone payments if paid, net of expenses and

adjustments, will be distributed to CVR holders pursuant to the CVR Agreement resulting from the Asset Acquisition.

14. Novation of Manufacturing Agreements

Pursuant to a Novation Agreement dated September 19, 2023 (the "Novation Agreement"), by and between the Company, Paragon and WuXi Biologics (Hong Kong) Limited ("WuXi Biologics"), the Company novated (i) a Biologics Master Services Agreement (the "WuXi Biologics MSA") and (ii) a Cell Line License Agreement (the "Cell Line License Agreement").

Biologics Master Services Agreement

In April 2023, Paragon and WuXi Biologics entered into the WuXi Biologics MSA, which was subsequently novated to the Company by Paragon on September 19, 2023 pursuant to the Novation Agreement. The WuXi Biologics MSA governs certain development activities and GMP manufacturing and testing for the SPY001 program, as well as potential future programs, on a work order basis. Under the WuXi Biologics MSA, the Company is obligated to pay WuXi Biologics a service fee and all non-cancellable obligations in the amount specified in each work order associated with the agreement for the provision of services.

The WuXi Biologics MSA terminates on the later of (i) June 20, 2027 or (ii) the completion of services under all work orders executed by the parties prior to June 20, 2027, unless terminated earlier. The term of each work order terminates upon completion of the services under such work order, unless terminated earlier. The Company can terminate the WuXi Biologics MSA or any work order at any time upon 30 days' prior written notice and immediately upon written notice if WuXi Biologics fails to obtain or maintain required material governmental licenses or approvals. Either party may terminate a work order (i) at any time upon six months prior notice with reasonable cause, provided however that if WuXi Biologics terminates a work order in such manner, no termination or cancellation fees shall be paid by the Company and (ii) immediately for cause upon (a) the other party's material breach that remains uncured for 30 days after notice of such breach, (b) the other party's bankruptcy or (c) a force majeure event that prevents performance for a period of at least 90 days.

Cell Line License Agreement

In April 2023, Paragon and WuXi Biologics entered into the Cell Line License Agreement, which was subsequently novated to the Company by Paragon pursuant to the Novation Agreement. Under the Cell Line License Agreement, the Company received a non-exclusive, worldwide, sublicensable license to certain of WuXi Biologics's know-how, cell line, biological materials (the "WuXi Biologics Licensed Technology") and media and feeds to make, have made, use, sell and import certain therapeutic products produced through the use of the cell line licensed by WuXi Biologics under the Cell Line License Agreement (the "WuXi Biologics Licensed Products"). Specifically, the WuXi Biologics Licensed Technology is used in certain manufacturing activities in support of the SPY001 program.

In consideration for the license, the Company agreed to pay WuXi Biologics a non-refundable license fee of $0.2 million. Additionally, if the Company manufactures all of its commercial supplies of bulk drug product with a manufacturer other than WuXi Biologics or its affiliates, the Company is required to make royalty payments to WuXi Biologics of less than one percent of global net sales of WuXi Biologics Licensed Products manufactured by a third-party manufacturer (the "Royalty"). If the Company manufactures part of its commercial supplies of the WuXi Biologics Licensed Products with WuXi Biologics or its affiliates, then the Royalty will be reduced accordingly on a pro rata basis.

The Cell Line License Agreement will continue indefinitely unless terminated (i) by the Company upon six months prior written notice and our payment of all undisputed amounts due to WuXi Biologics through the effective date of termination, (ii) by WuXi Biologics for a material breach by the Company that remains uncured for 60 days after written notice, (iii) by WuXi Biologics if the Company fails to make a payment and such failure continues for 30 days after receiving notice of such failure, or (iv) by either party upon the other party's bankruptcy.

15. Stock-Based Compensation

2015 Equity Incentive Plan

In March 2015, the Company adopted the 2015 Equity Incentive Plan (“2015 Plan”), administered by the board of directors, and provides for the Company to sell or issue share of Common Stock or restricted Common Stock, or to grant incentive stock options or nonqualified stock options for the purchase of Common Stock, to employees, members of the board of directors and consultants of the Company. Under the terms of the 2015 Plan, the exercise prices, vesting and other restrictions may be determined at the discretion of the board of directors, or their committee if so delegated, except that the exercise price per share of stock options may not be less than 100% of the fair market value of the share of common stock on the date of grant, the term of stock options may not be greater than ten years for all grants, and for grantees holding more than 10% of the total combined voting power of all classes of stock, the term may not be greater than five years.

The Company granted options under the 2015 Plan until April 2016 when it was terminated as to future awards, although it continues to govern the terms of options that remain outstanding under the 2015 Plan.

As of December 31, 2023, a total of 3,029 shares of Common Stock are subject to options outstanding under the 2015 Plan and will become available under the 2016 Equity Incentive Plan (“2016 Plan”) to the extent the options are forfeited or lapse unexercised.

2016 Equity Incentive Plan

The 2016 Plan became effective in April 2016 and serves as the successor to the 2015 Plan. Under the 2016 Plan, the Company may grant stock options, stock appreciation rights, restricted stock awards, restricted stock units, performance awards, and stock bonuses. The 2016 Plan provides for an initial reserve of 44,000 shares of Common Stock, plus 20,395 shares of Common Stock remaining under the 2015 Plan, and any share awards that subsequently are forfeited or lapse unexercised under the 2015 Plan. The shares reserved exclude shares of Common Stock reserved for issuance under the 2015 Plan.

In October 2018, the 2016 Plan was amended to increase the number of shares of Common Stock reserved for issuance thereunder by 70,384 shares, extend the term of the 2016 Plan through August 7, 2028, and provide for an automatic increase in the number of shares reserved for issuance thereunder on January 1 of each year for the remaining term of the plan equal to (a) 4.0% of the number of issued and outstanding shares of Common Stock on December 31 of the immediately preceding year, or (b) a lesser amount as approved by the board each year (the "Evergreen Provision"). As a result of the operation of each of these provisions, on January 1, 2023, 2022, and 2021, an additional 104,561, 78,968, and 76,735 shares, respectively, became available for issuance under the 2016 Plan.

In November 2023, the 2016 Plan was amended to (i) increase the number of shares of Common Stock reserved for issuance thereunder by 4,481,152 shares, (ii) revise the annual limit on non-employee director compensation from 4,000 shares to (a) $750,000 in total value or (b) $1,000,000 in the year of the director’s initial service as a non-employee director or in any year a director serves as chairman of the Board of Directors, in either case, applicable to fees paid in both cash and equity, (iii) remove the fixed termination date of the 2016 Plan and, (iv) revise the Evergreen Provision from 4% to 5% of issued and outstanding shares of Common Stock on December 31 of the preceding calendar year and to include shares issuable upon the exercise of pre-funded warrants and the conversion of outstanding shares of non-voting convertible preferred stock in the calculation.

As of December 31, 2023, the total number of shares reserved for issuance under the 2016 Plan was 5,019,177, of which 3,294,962 shares were subject to outstanding option awards and restricted unit awards.

2018 Equity Inducement Plan

In February 2018, the board of directors approved and adopted the 2018 Equity Inducement Plan (“2018 Plan”), which became effective on the same date. The board of directors approved an initial reserve of 44,000 shares of Common Stock to be used exclusively for individuals who were not previously employees or directors, or following a bona fide period of non-employment, as an inducement material to the individual entering into employment with the Company. Nonqualified stock options or restricted stock units may be granted

under the 2018 Plan at the discretion of the Compensation Committee or the board of directors. The Company did not seek stockholder approval of the 2018 Plan pursuant to Nasdaq Rule 5635(c)(4).

During 2023, the 2018 Plan was amended to increase the number of shares of Common Stock reserved for issuance by 6,000,000.

Under the 2016 Plan and 2018 Plan, the Company may grant stock-based awards with service conditions (“service-based” awards), performance conditions (“performance-based” awards), and market conditions (“market-based” awards). Service-based awards granted under the 2018 Plan, 2016 Plan, and 2015 Plan generally vest over four years and expire after ten years, although awards have been granted with vesting terms less than four years.

The Company granted 153,865 service-based restricted stock units (“RSUs”) during the year ended December 31, 2023 to certain employees under the 2018 Plan.

As of December 31, 2023, the total number of shares reserved for issuance under the 2018 Plan was 6,044,000, of which 5,350,595 shares were subject to outstanding awards.

Spyre 2023 Equity Incentive Plan

On June 22, 2023, in connection with the Asset Acquisition, the Company assumed the Amended and Restated Spyre 2023 Equity Incentive Plan (the "Spyre Equity Plan") and its outstanding and unexercised stock options, which were converted to options to purchase 2,734 shares of Common Stock. The acquisition-date fair value of these grants will be recognized as an expense on a pro-rata basis over the vesting period.

Parapyre Option Obligation

On June 22, 2023, in connection with the Asset Acquisition, the Company assumed the Parapyre Option Obligation which provided for an annual equity grant of warrants for Parapyre to purchase 1% of the then outstanding shares of Pre-Merger Spyre's common stock, on a fully diluted basis, on the last business day of each calendar year during the term of the Paragon Agreement, at the fair market value determined by the board of directors of Pre-Merger Spyre.

On September 29, 2023, the Company amended the Paragon Agreement to amend and restate certain terms of the option grant pertaining to the Parapyre Option Obligation, including but not limited to (i) defining that the annual equity grant of warrants is based on the outstanding shares of the Company’s Common Stock, (ii) establishing the grant date as the last business day of 2023 and 2024, and (iii) defining the term of the warrants granted as ten years. The Company determined that the 2023 and 2024 grants are two separate grants, as there would be no obligation for the 2024 grant had the Company exercised or terminated all of the options under the Paragon Agreement prior to December 31, 2023. The service inception period for the grant precedes the grant date, with the full award being vested as of the grant date with no post-grant date service requirement. Accordingly, a liability related to the Parapyre Option Obligation was recorded pursuant to the amended Paragon Agreement during 2023 interim periods. The Company determined that the grant date of the award was December 31, 2023, as all terms of the award, including number of shares and exercise price, were known by all parties. Accordingly, the Company measured the grant-date fair value of the warrants granted at approximately $11.5 million as an equity-classified award, of which $0.1 million was recognized as part of the liabilities assumed with the Asset Acquisition on June 22, 2023. For the year ended December 31, 2023, $11.4 million was recognized as stock compensation expense related to the Parapyre Option Obligation. There was no similar expense for the years ended December 31, 2022 and 2021.

As of December 31, 2023, the unamortized expense related to the Parapyre Option Obligation was nil.

The following table summarizes employee and non-employee stock option activity for the year ended December 31, 2023:

	Shares Issuable Under Options	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term	Aggregate Intrinsic Value
			(in years)	(in thousands)
Outstanding as of December 31, 2022	405,082	$ 113.75	6.72	$ 2
Granted	8,776,245	9.67		
Exercised	(46,246)	8.22		
Forfeited	(637,686)	43.00		
Outstanding as of December 31, 2023	8,497,395	$ 12.13	8.40	$ 98,928
Options vested and expected to vest as of December 31, 2023	8,497,395	$ 12.13	8.40	$ 98,928
Options exercisable as of December 31, 2023	1,065,700	$ 24.72	5.62	$ 13,328

The aggregate intrinsic value of options outstanding, exercisable, vested and expected to vest were calculated as the difference between the exercise price of the options and the fair value of the Company's Common Stock as of the reporting date.

For the years ended December 31, 2023, 2022, and 2021, the weighted-average grant date fair value of options granted was $9.67, $1.80, and $4.96, per share, respectively. The total intrinsic value of options exercised during the years ended December 31, 2023, and 2021 was $0.4 million and $0.7 million, respectively. No options were exercised in the year ended December 31, 2022.

There were 477,000 stock options issued to non-employees during the years ended December 31, 2023. There were no stock options issued to non-employees during the years ended December 31, 2022 and 2021. For the years ended December 31, 2023, 2022 and 2021, no non-employee stock options vested in the period.

2016 Employee Stock Purchase Plan

The 2016 Employee Stock Purchase Plan ("2016 ESPP") became effective in April 2016. A total of 6,600 shares of Common Stock were reserved for issuance under the 2016 ESPP. Eligible employees may purchase shares of Common Stock under the 2016 ESPP at 85% of the lower of the fair market value of the Common Stock as of the first or the last day of each offering period. Employees are limited to contributing 15% of the employee's eligible compensation and may not purchase more than $25,000 of stock during any calendar year. The 2016 ESPP will terminate ten years from the first purchase date under the plan, unless terminated earlier by the board of directors.

In June 2018, the 2016 ESPP was amended to provide for an automatic annual increase in the number of shares reserved for issuance thereunder on January 1 of each year for the remaining term of the year equal to (a) 1.0% of the number of issued and outstanding shares of Common Stock on December 31 of the immediately preceding year, or (b) a lesser amount as approved by the board of directors each year. As a result of the operation of this provision, on January 1, 2023, 2022 and 2021, an additional 26,140, 19,742, and 19,184 shares, respectively, became available for issuance under the 2016 ESPP. As of December 31, 2023, the reserve remaining and available for future issuance under the 2016 ESPP was 72,404 shares.

In February 2023, the 2016 ESPP was amended to increase the maximum shares purchased during any one period from 80 shares to 400 shares or a lesser amount determined by the board of directors.

For the year ended December 31, 2023, stock-based compensation expense related to the 2016 ESPP plan was di minimis. For the years ended 2022 and 2021, stock-based compensation expense related to the 2016 ESPP plan was $0.1 million and $0.2 million, respectively.

Restricted Common Stock Units

In July 2020, the Company granted 9,128 restricted stock units to certain employees, with vesting terms subject to regulatory, commercial, and clinical milestones, in addition to a service condition. As of December 31, 2023 none of these restricted stock units had vested and all restricted stock units were forfeited since the performance milestones were not met within the required time frame. No stock-based compensation expense was recognized on these awards.

The Company granted 153,865 service-based restricted stock units during the year ended December 31, 2023. There were no restricted stock units granted during the years ended December 31, 2022 and 2021.

The following table summarizes employee restricted stock activity for the year ended December 31, 2023:

	Shares	Weighted Average Grant Date Fair Value
Unvested restricted stock units as of December 31, 2022	5,660	$ 203.25
Granted	153,865	18.17
Vested	—	—
Forfeited	(5,660)	203.25
Unvested restricted stock units as of December 31, 2023	153,865	$ 18.17

There were no restricted stock units granted to non-employees during the years ended December 31, 2023, 2022, and 2021.

Stock-Based Compensation Expense

Total stock-based compensation expense recognized from the Company's equity incentive plans, 2018 Plan, and the 2016 ESPP for the years ended December 31, 2023, 2022, and 2021 was as follows (in thousands):

	Year Ended December 31,					
	2023		2022		2021	
	Employees	Non-Employees	Employees	Non-Employees	Employees	Non-Employees
Research and development	$ 2,910	$ 11,328	$ 2,591	$ —	$ 2,723	$ —
General and administrative	11,327	109	4,520	—	5,315	—
Total stock-based compensation expense	$ 14,237	$ 11,437	$ 7,111	$ —	$ 8,038	$ —

No related tax benefits were recognized for the years ended December 31, 2023, 2022, and 2021 (see Note 18).

The employee and non-employee awards contain both performance and service-based vesting conditions. No expense was recognized for the unvested employee and non-employee awards with only a performance condition for the years ended December 31, 2023, 2022, and 2021. The performance-based vesting conditions represent specific performance targets. Compensation expense for employee and non-employee share-based payment awards with performance conditions is recognized when the performance condition is deemed probable of achievement.

As of December 31, 2023, the Company had an aggregate of $64.4 million of unrecognized stock-based compensation expense for options outstanding, which is expected to be recognized over a weighted average period of 3.5 years.

In determining the fair value of the stock-based awards, the Company uses the Black-Scholes option-pricing model and assumptions discussed below. Each of these inputs is subjective and generally requires significant judgment to determine.

Expected Term

The Company's expected term represents the period that the Company's stock-based awards are expected to be outstanding and is determined using the simplified method (based on the midpoint between the vesting date and the end of the contractual term). The Company utilizes this method due to lack of historical exercise data and the plain-vanilla nature of the Company's stock-based awards.

Expected Volatility

Since the Company was privately held through April 2016 and transitioned from a clinical stage company to a pre-clinical stage company in 2023, it alone does not have the relevant company-specific historical data to support its expected volatility. As such, the Company has used an average of expected volatilities based on the volatilities of a representative group of publicly traded biopharmaceutical companies over a period equal to the expected term of the stock option grants. Subsequent to the Company's initial public offering, it began to consider the Company's own historic volatility. However, due to the transition from a clinical stage company to a pre-clinical stage company, the Company still uses peer company data to assist in this analysis. For purposes of identifying comparable companies, the Company selected companies with comparable characteristics to it, including enterprise value, risk profiles, position within the industry, and with historical share price information sufficient to meet the expected life of the stock-based awards. The historical volatility data was computed using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of the stock-based awards. The Company intends to consistently apply this process using the same or similar comparable entities until a sufficient amount of historical information regarding the volatility of the Company's own share price post transition becomes available.

Risk-Free Interest Rate

The risk-free interest rate is based on the U.S. Treasury zero coupon issues in effect at the time of grant for periods corresponding with the expected term of option.

Expected Dividend

The Company has never paid dividends on its Common Stock and has no plans to pay dividends on its Common Stock. Therefore, the Company used an expected dividend yield of zero.

Valuation of Stock Options and 2016 ESPP

The fair value of the stock options granted under the the Company's equity incentive plans, as well as the shares available for purchase under the 2016 ESPP were determined using the Black-Scholes option-pricing model. The following table summarizes the weighted-average assumptions used in calculating the fair value of the awards:

	Year Ended December 31,		
	2023	2022	2021
Stock Options Granted			
Expected term (in years)	5.88	6.00	5.99
Expected volatility	107 %	84 %	83 %
Risk-free interest	4.37 %	2.93 %	0.88 %
Dividend yield	0 %	0 %	0 %
2016 ESPP			
Expected term (in years)	0.49	0.49	0.50
Expected volatility	181 %	84 %	86 %
Risk-free interest	4.99 %	1.95 %	0.08 %
Dividend yield	0 %	0 %	0 %

16. Defined Contribution Plan

The Company sponsors a 401(k) retirement plan in which substantially all of its full-time employees are eligible to participate. Participants may contribute a percentage of their annual compensation to this plan, subject to statutory limitations. During the years ended December 31, 2023, 2022, 2021, the Company provided $0.2 million, $0.6 million, and $0.6 million, respectively, in contributions to the plan.

17. Restructuring Charges

Severance and Stock Compensation

On April 12, 2023, based on the review of the inconclusive interim results from the Company's Phase 1/2 clinical trial of pegtarviliase for the treatment of classical homocystinuria and other business considerations, the Company announced that it had initiated a process to explore strategic alternatives to maximize stockholder value and engaged an independent exclusive financial advisor to support this process.

As a result, the Company implemented a restructuring plan resulting in an approximate 83% reduction of the Company’s existing headcount by June 30, 2023. The Company recognized restructuring expenses consisting of cash severance payments and other employee-related costs of $6.4 million during the year ended December 31, 2023. Cash payments for employee related restructuring charges of $5.3 million were paid as of December 31, 2023. In addition, the Company recognized $1.0 million in non-cash stock-based compensation expense related to the accelerated vesting of stock-based awards for certain employees. The Company recorded these restructuring charges based on each employee’s role to the respective research and development and general and administrative operating expense categories on its consolidated statements of operations and comprehensive loss.

The following table summarizes the changes in the Company's accrued restructuring balance (in thousands):

	Beginning Balance December 31, 2022	Charges	Payments	Ending Balance December 31, 2023
Severance liability	$ —	$ 6,448	$ (5,325)	$ 1,123

Sale of Assets

During the second quarter of 2023, the Company sold various lab equipment, consumables, and furniture and fixtures for total consideration of $0.5 million. After recording the disposal of all the Company's property and equipment net of proceeds, the Company recorded a $0.7 million and $0.2 million loss on disposal of long lived assets which is included in Research and development and General and administrative expenses, respectively.

Lease Right-of-use Asset and Leasehold Improvement Impairment

Effective June 30, 2023, the Company abandoned its leased office space in Austin, Texas. As a result, the Company recognized an impairment loss of $0.9 million related to the operating lease right-of-use asset and $1.7 million related to leasehold improvements. On August 7, 2023, the Company terminated its building lease in Austin, Texas. The negotiated termination agreement obligated the Company to pay the lessor a $2.0 million termination fee in exchange for releasing the Company of all further obligations under the lease.

All charges related to the restructuring activities were recognized during the second quarter of 2023. No further restructuring charges will be incurred under the restructuring plan. A summary of the charges related to the restructuring activities is as follows (in thousands):

	Severance Related Expenses	Stock Compensation Expenses	Loss on Disposal of Long Lived Assets	Lease Asset Impairment	Total Restructuring Costs
Research and development	$ 3,182	$ 123	$ 749	$ 1,405	$ 5,459
General and administrative	3,266	870	182	1,175	5,493
Total	$ 6,448	$ 993	$ 931	$ 2,580	$ 10,952

18. Income Taxes

The following table summarizes the (loss) income before income tax expense by jurisdiction for the periods indicated:

	Year Ended December 31,		
	2023	2022	2021
Domestic	$ (338,942)	$ (84,113)	$ (65,940)
Foreign	126	162	280
Loss before income tax expense	$ (338,816)	$ (83,951)	$ (65,660)

For the year ended December 31, 2023, the Company recognized no provision or benefit from income taxes. For both the years ended December 31, 2022 and 2021, the Company recognized an income tax expense of $0.1 million, related to foreign subsidiaries income tax expense and the Texas margins tax. The difference between the Company's provision for income taxes and the amounts computed by applying the statutory federal income tax rate to income before income taxes is as follows (in thousands):

	Year Ended December 31,		
	2023	2022	2021
Tax provision derived by applying the federal statutory rate to income before income taxes	$ (71,151)	$ (17,630)	$ (13,789)
Loss on forward contract valuation	17,541	—	—
Acquired IPR&D	27,340	—	—
Loss on CVR revaluation	3,987	—	—
Other permanent differences	4,472	1,042	1,002
Federal tax credits	(1)	(3,559)	(3,815)
State tax credits	—	(640)	(152)
Effect of tax rate on foreign jurisdiction	(53)	42	(5)
Change in the valuation allowance	17,839	20,609	16,900
Income tax (benefit) expense	$ (26)	$ (136)	$ 141

The components of the deferred tax assets and liabilities consist of the following (in thousands):

	December 31,	
	2023	2022
Deferred tax assets		
Net operating loss carryforward	$ 74,454	$ 68,917
Capitalized 174 R&D costs	22,532	11,097
Intangible assets	47	52
Deferred revenue	—	566
Accrued expense	579	668
Stock-based compensation	4,246	3,293
Federal tax credits	21,914	21,914
State tax credits	1,631	1,631
Other	88	190
Total deferred tax assets	125,491	108,328
Deferred tax liabilities		
Depreciable assets	—	(676)
Total deferred tax liabilities	—	(676)
Less: Valuation allowance	(125,491)	(107,652)
Deferred tax assets, net	$ —	$ —

The Company has established a full federal and state valuation allowance equal to the net deferred tax assets due to uncertainties regarding the realization of the deferred tax asset based on the Company's lack of earnings history. The valuation allowance increased by $17.8 million, $20.6 million, and $16.9 million during the years ended December 31, 2023, 2022, and 2021, respectively, primarily due to continuing loss from operations.

As of December 31, 2023 and 2022, the Company had U.S. net operating loss carryforwards ("NOL") of $354.5 million and $328.2 million, respectively. For both the years ended December 31, 2023 and 2022, the Company had U.S. tax credit carryforwards and state tax credit carryforwards of $21.9 million and $1.6 million, respectively. Of the net operating loss and tax credit carryforwards $58.4 million and $21.9 million, respectively,

will expire in 2033, if not utilized. Any remaining net operating loss will carry forward indefinitely and can be utilized to offset up to 80% of the taxable income in any tax year. The net operating loss and credit carryforwards are subject to Internal Revenue Service adjustments until the statute closes on the year the net operating loss or tax credits are utilized.

The Company has not completed a study to assess whether an ownership change has occurred or whether there have been multiple ownership changes since the Company's formation due to the complexity and cost associated with such a study, and the fact that there may be additional such ownership changes in the future. If the Company has experienced an ownership change at any time since its formation, utilization of the NOL or research and development credit carryforwards would be subject to an annual limitation under Section 382 or 383 of the Internal Revenue Code, which is determined by first multiplying the value of the Company's stock at the time of the ownership change by the applicable long-term, tax-exempt rate, and then could be subject to additional adjustments, as required. Additionally, the separate return limitation year ("SRLY") rules may apply to losses of the Company's eight wholly owned U.S. subsidiary corporations. The SRLY rules limit the consolidated group's use of a subsidiary corporation's net operating losses to the amount of income generated by the subsidiary corporation after it becomes a member of the group. Any limitation may result in expiration of a portion of the NOL or research and development credit carryforwards before utilization. Further, until a study is completed and any limitation known, no amounts are being considered as an uncertain tax position or disclosed as an unrecognized tax benefit. Additionally, the Company does not expect any unrecognized tax benefits to change significantly over the next twelve months. Due to the existence of the valuation allowance, future changes in the Company's unrecognized tax benefits will not impact its effective tax rate. Any carryforwards that will expire prior to utilization as a result of such limitations will be removed from deferred tax assets with a corresponding reduction of the valuation allowance.

The Company is subject to examination by taxing authorities in its significant jurisdictions for the 2019 and subsequent years. However, due to NOL and tax attribute carryovers, the taxing authorities have the ability to adjust the NOLs and other tax attributes related to closed years. As of December 31, 2023 and 2022, there were no amounts recorded for uncertain tax positions. As of December 31, 2023, undistributed earnings of the Company's incorporated foreign subsidiaries are immaterial. Under the Global Intangible Low-Taxed Income ("GILTI") provisions of the 2017 Tax Cuts and Jobs Act, U.S. income taxes have been incurred on the undistributed earnings of the foreign subsidiaries and therefore, the tax impact upon distribution is limited to state income and withholding taxes and is not material.

19. Net Loss Per Share

The Company computes net loss attributable per common stockholder using the two-class method required for participating securities. The Company considers convertible preferred stock to be participating securities. In the event that the Company paid out distributions, holders of convertible preferred stock would participate in the distribution.

The two-class method is an earnings (loss) allocation method under which earnings (loss) per share is calculated for Common Stock and participating security considering a participating security's rights to undistributed earnings (loss) as if all such earnings (loss) had been distributed during the period. The holders of Series A Preferred Stock and Series B Preferred Stock do not have an obligation to fund losses and therefore the Series A Preferred Stock and the Series B Preferred Stock were excluded from the calculation of basic net loss per share.

Basic and diluted net loss per share is computed by dividing the net loss by the weighted-average number of Common Stock and pre-funded warrants outstanding during the period, without consideration of potential dilutive securities. The pre-funded warrants are included in the computation of basic net loss per share as the exercise price is negligible and they are fully vested and exercisable. For periods in which the Company generated a net loss, the Company does not include the potential impact of dilutive securities in diluted net loss per share, as the impact of these items is anti-dilutive. The Company has generated a net loss for all periods presented, therefore diluted net loss per share is the same as basic net loss per share since the inclusion of potentially dilutive securities would be anti-dilutive.

The following weighted-average equity instruments were excluded from the calculation of diluted net loss per share because their effect would have been anti-dilutive for the periods presented:

	Year Ended December 31,		
	2023	2022	2021
Options to purchase Common Stock	2,583,226	346,331	264,858
Unvested restricted stock units	4,240	6,983	7,975
Outstanding Parapyre Warrants	5,625	—	—

The following is a reconciliation of the shares used as the denominator for the calculation of basic and diluted net loss per share:

	Year Ended December 31,		
	2023	2022	2021
Weighted average Common Shares	6,201,954	2,307,668	1,956,933
Weighted average pre-funded warrants	695,111	1,063,563	672,851
Total basic and diluted weighted average shares	6,897,065	3,371,231	2,629,784

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 principal executive officer and our principal financial officer, evaluated, as of the end of the period covered by this Annual Report on Form 10-K, the effectiveness of our disclosure controls and procedures. Based on that evaluation of our disclosure controls and procedures as of December 31, 2023, our principal executive officer and principal financial officer concluded that our disclosure controls and procedures as of such date were effective at the reasonable assurance level. 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 (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 us in the reports we file or submit under the Exchange Act is accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate to allow timely decisions regarding required disclosure. 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.

Management’s Annual Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, our principal executive and principal financial officers and effected by our 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 U.S. GAAP. Our internal control over financial reporting includes those policies and procedures that:

- pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect our transactions and dispositions of our assets;
- provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with U.S. GAAP, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and
- provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on our financial statements.

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

Our management, with the participation of our principal executive officer and principal financial officer, assessed the effectiveness of our internal control over financial reporting as of December 31, 2023. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in its 2013 Internal Control – Integrated Framework. Based on our assessment, our management has concluded that, as of December 31, 2023, our internal control over financial reporting was effective based on those criteria.

This Annual Report on Form 10-K does not include an attestation report of our independent registered public accounting firm regarding internal control over financial reporting. For as long as we remain a “smaller reporting company” as defined by Rule 12b-2 of the Exchange Act and report less than $100 million of annual revenues in our most recent fiscal year, we intend to take advantage of the exemption permitting us not to comply with the requirement that our independent registered public accounting firm provide an attestation on the effectiveness of our internal control over financial reporting.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting that occurred during the quarter ended December 31, 2023 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

(b) None of our directors or executive officers adopted or terminated a Rule 10b5-1 trading arrangement or a non-Rule 10b5-1 trading arrangement during the quarter ended December 31, 2023, as such terms are defined under Item 408(a) of Regulation S-K.

ITEM 9C. DISCLOSURE REGARDING FOREIGN JURISDICTIONS THAT PREVENT INSPECTIONS

None.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by this item is incorporated herein by reference from the applicable information set forth in “the Proxy Statement with respect to our 2024 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year covered by this Annual Report on Form 10-K (the “2024 Proxy Statement”), including the sections titled “Information Regarding Director Nominees and Continuing Directors,” “Executive Officers,” “Corporate Governance,” and, if applicable, “Delinquent Section 16(a) Reports.”

ITEM 11. EXECUTIVE COMPENSATION

The information required by this item is incorporated herein by reference from the applicable information set forth in our 2024 Proxy Statement, including the sections titled “Executive Compensation” and "Corporate Governance."

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information required by this item is incorporated herein by reference from the applicable information set forth in our 2024 Proxy Statement, including the sections titled “Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters” and “Securities Authorized for Issuance Under Equity Compensation Plans.”

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

The information required by this item is incorporated herein by reference from the applicable information set forth in our 2024 Proxy Statement, including the sections titled “Certain Relationships and Related Party Transactions and "Director Independence."

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES

The information required by this item is incorporated herein by reference from the applicable information set forth in our 2024 Proxy Statement, including the section titled “Ratification of Independent Auditor Appointment."

PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

The following documents are filed as part of this report:

1. Financial Statements

See Index to Financial Statements at Item 8 herein.

2. Financial Statement Schedules

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

3. Exhibits

Exhibit Number	Description of Document	Incorporate by Reference				Filed Herewith
		Form	File No.	Date of Filing	Exhibit No.	
2.1	Agreement and Plan of Merger, dated June 22, 2023, by and among the Company, Aspen Merger Sub I, Inc., Sequoia Merger Sub II, LLC and Spyre Therapeutics, Inc.	S-1/A	333-276251	2/5/2024	2.1	
3.1	Amended and Restated Certificate of Incorporation	S-1/A	333-276251	2/5/2024	3.1	
3.2	Amended and Restated Bylaws	S-1/A	333-276251	2/5/2024	3.2	
3.3	Certificate of Designations of Series A Non-Voting Convertible Preferred Stock	S-1/A	333-276251	2/5/2024	3.3	
3.4	Certificate of Designations of Series B Non-Voting Convertible Preferred Stock	S-1/A	333-276251	2/5/2024	3.4	
4.1	Form of Registration Rights Agreement, by and among the Company and certain purchasers (December 2023 PIPE)	S-1/A	333-276251	2/5/2024	4.1	
4.2	Form of Common Stock Certificate	S-1/A	333-276251	2/5/2024	4.2	
4.3	Securities Purchase Agreement, dated December 7, 2023, by and among Spyre Therapeutics, Inc. and each purchaser identified on Annex A thereto	S-1/A	333-276251	2/5/2024	4.3	
4.4	Form of Registration Rights Agreement, by and among the Company and certain purchasers (June 2023 PIPE)	S-1/A	333-276251	2/5/2024	4.4	
4.5	Description of the Registrant's securities					X
4.6	Form of Pre-Funded Warrants 2022	S-1/A	333-276251	2/5/2024	4.5	
10.1	Form of Indemnification Agreement	S-1/A	333-276251	2/5/2024	10.19	
10.2‡	2015 Equity Incentive Plan and forms of award agreements	S-1/A	333-276251	2/5/2024	10.7	

Exhibit Number	Description of Document	Incorporate by Reference				Filed Herewith
		Form	File No.	Date of Filing	Exhibit No.	
10.3‡	Spyre Therapeutics, Inc. 2016 Equity Incentive Plan, As Amended and Restated Effective November 21, 2023	S-1/A	333-276251	2/5/2024	10.8	
10.4‡	Spyre Therapeutics, Inc. 2016 Employee Stock Purchase Plan, as amended by the First Amendment on January 31, 2024					X
10.5‡	Spyre Therapeutics, Inc. 2018 Equity Inducement Plan and the First Amendment, Second Amendment, Third Amendment and Fourth Amendment thereto	S-1/A	333-276251	2/5/2024	10.10	
10.6‡	Form of Stock Option Agreement under the Amended and Restated 2018 Equity Inducement Plan	S-1/A	333-276251	2/5/2024	10.11	
10.7‡	Spyre Therapeutics, Inc. 2023 Equity Incentive Plan	S-1/A	333-276251	2/5/2024	10.12	
10.8‡	Form of Stock Restriction Agreement	S-1/A	333-276251	2/5/2024	10.13	
10.9‡	Form of Severance Agreement	S-1/A	333-276251	2/5/2024	10.14	
10.10†	Biologics Master Services Agreement, effective June 20, 2022, by and between Paragon Therapeutics, Inc. and WuXi Biologics (Hong Kong) Limited	S-1/A	333-276251	2/5/2024	10.1	
10.11†	Cell Line License Agreement, effective June 20, 2022, by and between Paragon Therapeutics, Inc. and WuXi Biologics (Hong Kong) Limited	S-1/A	333-276251	2/5/2024	10.2	
10.12	Novation Agreement, dated September 19, 2023, by and between Paragon Therapeutics, Inc., the Company and WuXi Biologics (Hong Kong) Limited	S-1/A	333-276251	2/5/2024	10.3	
10.13‡	Amended and Restated Offer Letter, dated November 22, 2023 and as amended on February 1, 2024, by and between the Company and Cameron Turtle	S-1/A	333-276251	2/5/2024	10.4	
10.14†	Amended and Restated Antibody Discovery and Option agreement, dated September 29, 2023, by and between Paragon Therapeutics, Inc., Parapyre Holding LLC and Spyre Therapeutics, LLC	S-1/A	333-276251	2/5/2024	10.5	
10.15‡	Separation and Consulting Agreement and General Release of Claims by and between the Company and Jonathan Alspaugh, dated as of September 22, 2023	S-1/A	333-276251	2/5/2024	10.15	
10.16‡	Offer Letter, dated August 10, 2023, by and between the Company and Scott Burrows	S-1/A	333-276251	2/5/2024	10.16	
10.17	Asset Purchase Agreement, dated July 27, 2023, by and between the Company and Immedica Pharma AB	S-1/A	333-276251	2/5/2024	10.17	

Exhibit Number	Description of Document	Incorporate by Reference				Filed Herewith
		Form	File No.	Date of Filing	Exhibit No.	
10.18	Lease Termination Agreement dated August 7, 2023, between the Company and Las Cimas Owner LP	S-1/A	333-276251	2/5/2024	10.18	
10.19‡	Offer Letter, dated August 18, 2023, by and between the Company and Heidy King-Jones					X
10.20	Consulting Agreement by and between the Company and Mark McKenna, effective August 1, 2023					X
21.1	Subsidiaries of the Registrant					X
23.1	Consent of PricewaterhouseCoopers LLP					X
24.1	Power of Attorney. Reference is made to the signature page hereto					X
31.1	Certification of the Principal Executive Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934					X
31.2	Certification of the Principal Financial Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934					X
32.1	Certification of the Principal Executive Officer and Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002					X
97	Spyre Therapeutics, Inc. Compensation Recoupment (Clawback) Policy					X
101.INS	Inline XBRL Instance Document - the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document					X
101.SCH	Inline XBRL Taxonomy Extension Schema Document					X
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document					X
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document					X
101.LAB	Inline XBRL Taxonomy Extension Labels Linkbase Document					X
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document					X

Exhibit Number	Description of Document	Incorporate by Reference				Filed Herewith
		Form	File No.	Date of Filing	Exhibit No.	
104	The cover page of this Annual Report on Form 10-K for the year ended December 31, 2023, formatted in Inline XBRL and contained in Exhibit 101					

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

‡ Indicates management contract or compensatory plan.

(1) The certifications on Exhibit 32 hereto are deemed not "filed" for purposes of Section 18 of the Exchange Act or otherwise subject to the liability of that Section. Such certifications will not be deemed incorporated by reference into any filing under the Securities Act or the Exchange Act, regardless of any general incorporation language contained in such filing.

ITEM 16. FORM 10-K SUMMARY

None.

SIGNATURES

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

Date: February 29, 2024

SPYRE THERAPEUTICS, INC.

By: /s/ Scott Burrows

Scott Burrows

Chief Financial Officer

(Principal Financial Officer and Principal Accounting Officer)

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Dr. Cameron Turtle and Mr. Scott Burrows, jointly and severally, his or her attorneys-in-fact, each with the power of substitution, for him or her in any and all capacities, to sign any amendments to this Report on Form 10-K and to file same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each of said attorneys-in-fact, or his substitutes, may do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this Report has been signed below by the following persons on behalf of the Registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Cameron Turtle, D.Phil Cameron Turtle, D.Phil	President and Chief Executive Officer and Director (Principal Executive Officer)	February 29, 2024
/s/ Scott Burrows Scott Burrows	Chief Financial Officer (Principal Financial Officer and Principal Accounting Officer)	February 29, 2024
/s/ Russell J. Cox Russell J. Cox	Chairman of the Board	February 29, 2024
/s/ Jeffrey W. Albers Jeffrey W. Albers	Director	February 29, 2024
/s/ Peter Harwin Peter Harwin	Director	February 29, 2024
/s/ Michael Henderson, M.D. Michael Henderson, M.D.	Director	February 29, 2024
/s/ Tomas Kiselak Tomas Kiselak	Director	February 29, 2024
/s/ Mark McKenna Mark McKenna	Director	February 29, 2024
/s/ Laurie Stelzer Laurie Stelzer	Director	February 29, 2024

Exhibit 4.5

DESCRIPTION OF CAPITAL STOCK

General

The following description summarizes the material terms of the capital stock of Spyre Therapeutics, Inc. ("we," "us," "our" or the "company"), as well as other material terms of our amended and restated certificate of incorporation ("Certificate of Incorporation") and amended and restated bylaws ("Bylaws") and certain provisions of Delaware law. This summary does not purport to be complete and is qualified in its entirety by the provisions of our Certificate of Incorporation and Bylaws, copies of which are filed as exhibits to our Annual Report on Form 10-K, to which this exhibit is also appended.

Our authorized capital stock consists of 400,000,000 shares of common stock, $0.0001 par value per share ("Common Stock"), and 10,000,000 shares of preferred stock, $0.0001 par value per share ("Preferred Stock"), of which 1,086,341 shares have been designated as Series A Non-Voting Convertible Preferred Stock, $0.0001 par value per share ("Series A Preferred Stock") and 150,000 shares have been designated as Series B Non-Voting Convertible Preferred Stock, $0.0001 par value per share ("Series B Preferred Stock").

Common Stock

Our Certificate of Incorporation authorizes the issuance of up to 400,000,000 shares of Common Stock. All outstanding shares of Common Stock are validly issued, fully paid and nonassessable.

Dividend rights

Subject to preferences that may apply to any shares of Preferred Stock outstanding at the time, the holders of our Common Stock are entitled to receive dividends out of funds legally available if our board of directors, in its discretion, determines to issue dividends and then only at the times and in the amounts that our board of directors may determine.

Voting rights

Holders of our Common Stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders. We have not provided for cumulative voting for the election of directors in our Certificate of Incorporation. Accordingly, pursuant to our Certificate of Incorporation, holders of a majority of the shares of our Common Stock are able to elect all of our directors. Our Certificate of Incorporation establishes a classified board of directors, divided into three classes with staggered three-year terms. Only one class of directors will be elected at each annual meeting of our stockholders, with the other classes continuing for the remainder of their respective three-year terms.

No preemptive or similar rights

Our Common Stock is not entitled to preemptive rights, and is not subject to conversion, redemption or sinking fund provisions.

Right to receive liquidation distributions

Upon our liquidation, dissolution or winding-up, the assets legally available for distribution to our stockholders would be distributable ratably among the holders of our Common Stock and any participating Preferred Stock outstanding at that time, subject to prior satisfaction of all outstanding debt and liabilities and the preferential rights of and the payment of liquidation preferences, if any, on any outstanding shares of Preferred Stock.

Preferred Stock

Under the terms of our Certificate of Incorporation, our board of directors is authorized, subject to limitations prescribed by Delaware law, to issue up to 10,000,000 shares of Preferred Stock in one or more series, to establish from time to time the number of shares to be included in each series and to fix the designation, powers, preferences and rights of the shares of each series and any of their qualifications, limitations or restrictions, in each case without further vote or action by our stockholders. Subject to any certificates of designation, our board of directors can also increase or decrease the number of shares of any series of Preferred Stock, but not below the number of shares of that series then outstanding, without any further vote or action by our stockholders. Our board of directors may authorize the issuance of Preferred Stock with voting or conversion rights that could adversely affect the voting power or other rights of the holders of our Common Stock. The issuance of Preferred Stock, while providing flexibility in connection with possible acquisitions and other corporate purposes, could, among other things, have the effect of delaying, deferring or preventing a change in control of our company and might adversely affect the market price of our Common Stock and the voting and other rights of the holders of our Common Stock.

Registration Rights

Certain holders of our Common Stock, Series A Preferred Stock and Series B Preferred Stock are entitled to certain rights with respect to the registration of such securities pursuant to the terms of certain Registration Rights Agreements between us and certain holders of our Common Stock, Series A Preferred Stock and/or Series B Preferred Stock. Under the terms of the Registration Rights Agreements, we have filed registration statements to sell registrable securities. We are required to use commercially reasonable efforts to effect a registration of such shares. The Registration Rights Agreements do not include demand registration rights or piggyback registration rights. All fees, costs and expenses of underwritten registrations under these agreements will be borne by us and all selling expenses, including underwriting discounts and selling commissions, will be borne by the holders of the shares being registered.

Anti-Takeover Provisions

The provisions of Delaware law, our Certificate of Incorporation and our Bylaws could have the effect of delaying, deferring or discouraging another person from acquiring control of our company. These provisions, which are summarized below, may have the effect of discouraging takeover bids. They are also designed, in part, to encourage persons seeking to acquire control of us to negotiate first with our board of directors. We believe that the benefits of increased protection of our potential ability to negotiate with an unfriendly or unsolicited acquirer outweigh the disadvantages of discouraging a proposal to acquire us because negotiation of these proposals could result in an improvement of their terms.

Delaware law

We are subject to the provisions of Section 203 of the Delaware General Corporation Law (the "DGCL") regulating corporate takeovers. In general, Section 203 prohibits a publicly-held Delaware corporation from engaging in a business combination with an interested stockholder for a period of three years following the date on which the person became an interested stockholder unless:

- prior to the date of the transaction, the board of directors of the corporation approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;

- upon completion of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding upon consummation of the transaction, excluding for purposes of determining the voting stock outstanding, but not the outstanding voting stock owned by the interested stockholder, (1) shares owned by persons who are directors and also officers and (2) shares owned by employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or

- At or subsequent to the date of the transaction, the business combination is approved by the board of directors of the corporation and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66 2/3% of the outstanding voting stock which is not owned by the interested stockholder.

Section 203 defines a "business combination" to include:

- any merger or consolidation involving the corporation and the interested stockholder;
- any sale, transfer, pledge or other disposition involving the interested stockholder of 10% or more of the assets of the corporation;
- subject to exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;
- any transaction involving the corporation that has the effect of increasing the proportionate share of the stock of any class or series of the corporation beneficially owned by the interested stockholder; and
- the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

In general, Section 203 defines an "interested stockholder" as an entity or person who, together with the person's affiliates and associates, beneficially owns, or within three years prior to the time of determination of interested stockholder status did own, 15% or more of the outstanding voting stock of the corporation.

Certificate of Incorporation and Bylaw Provisions

Our Certificate of Incorporation and our Bylaws include a number of provisions that could deter hostile takeovers or delay or prevent changes in control of our company, including the following:

- ***Board of Directors vacancies***. Our Certificate of Incorporation and Bylaws authorize our board of directors to fill vacant directorships, including newly created seats unless the board of directors determines that any such vacancies shall be filled by the stockholders. In addition, the number of directors constituting our board of directors is permitted to be set only by a resolution adopted by a majority vote of our entire board of directors. These provisions prevent a stockholder from increasing the size of our board of directors and then gaining control of our board of directors by filling the resulting vacancies with its own nominees. This makes it more difficult to change the composition of our board of directors but promotes continuity of management.
- ***Classified board***. Our Certificate of Incorporation provides that our board is classified into three classes of directors, each with staggered three-year terms. A third party may be discouraged from making a tender offer or otherwise attempting to obtain control of us as it is more difficult and time consuming for stockholders to replace a majority of the directors on a classified board of directors.
- ***Stockholder action; special meetings of stockholders***. Our Certificate of Incorporation and Bylaws provide that our stockholders may not take action by written consent, but may only take action at annual or special meetings of our stockholders. As a result, a holder controlling a majority of our capital stock would not be able to amend our Bylaws or remove directors without holding a meeting of our stockholders called in accordance with our Bylaws. Further, our Certificate of Incorporation and
  Bylaws provide that special meetings of our stockholders may be called only by a majority of our entire board of directors, the chairperson of our board of directors, our Chief Executive Officer or our President, thus prohibiting a stockholder from calling a special meeting. These provisions might delay the ability of our stockholders to force consideration of a proposal or for stockholders controlling a majority of our capital stock to take any action, including the removal of directors.

- ***Advance notice requirements for stockholder proposals and director nominations***. Our Bylaws provide advance notice procedures for stockholders seeking to bring business before our annual meeting of stockholders or to nominate candidates for election as directors at our annual meeting of stockholders. Our Bylaws also specify certain requirements regarding the form and content of a stockholder's notice. These provisions might preclude our stockholders from bringing matters before our annual meeting of stockholders or from making nominations for directors at our annual meeting of stockholders if the proper procedures are not followed. We expect that these provisions might also discourage or deter a potential acquirer from conducting a solicitation of proxies to elect the acquirer's own slate of directors or otherwise attempting to obtain control of our company.

- ***No cumulative voting***. The DGCL provides that stockholders are not entitled to the right to cumulate votes in the election of directors unless a corporation's certificate of incorporation provides otherwise. Our Certificate of Incorporation and Bylaws do not provide for cumulative voting.

- ***Directors removed only for cause***. Our Certificate of Incorporation provides that stockholders may remove directors only for cause.

- ***Amendment of charter provisions***. Any amendment of the above provisions in our Certificate of Incorporation requires approval by holders of at least two-thirds of our outstanding Common Stock, provided that if two-thirds of our entire board of directors approves such an amendment, then only the approval of a majority of holders is required.

- ***Issuance of Preferred Stock***. Our board of directors has the authority, without further action by the stockholders, to issue up to 10,000,000 shares of Preferred Stock with rights and preferences, including voting rights, designated from time to time by our board of directors. The existence of authorized but unissued shares of Preferred Stock enables our board of directors to render more difficult or to discourage an attempt to obtain control of us by merger, tender offer, proxy contest or other means.

- ***Choice of forum***. Our Certificate of Incorporation and Bylaws provide that the Court of Chancery of the State of Delaware is the sole and exclusive forum for any derivative action or proceeding brought on our behalf; any action asserting a breach of fiduciary duty; any action asserting a claim against us arising pursuant to the DGCL, our Certificate of Incorporation or our Bylaws; or any action asserting a claim against us that is governed by the internal affairs doctrine. In addition, our Bylaws also provide that the federal district courts of the United States is the exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act. These choice of forum provisions will not apply to claims brought to enforce a duty or liability created by the Exchange Act.

Transfer Agent and Registrar

The transfer agent and registrar for our Common Stock, our Series A Preferred Stock and our Series B Preferred Stock is Equiniti Trust Company, LLC (previously known as American Stock Transfer & Trust Company LLC). The transfer agent's address is 6201 15th Avenue, Brooklyn, New York 11219, and its telephone number is (800) 937-5449.

Exchange Listing

Our Common Stock is listed on The Nasdaq Global Select Market under the symbol "SYRE."

Exhibit 10.4

SPYRE THERAPEUTICS, INC.
2016 EMPLOYEE STOCK PURCHASE PLAN

(as amended by the First Amendment on January 31, 2024)

1. PURPOSE. Spyre Therapeutics, Inc. has adopted this Plan effective as of the date of the IPO. The purpose of this Plan is to provide eligible employees of the Company and the Participating Corporations with a means of acquiring an equity interest in the Company and to enhance such employees' sense of participation in the Company's affairs. Capitalized terms not defined elsewhere in the text are defined in Section 28.

2. ESTABLISHMENT OF PLAN. The Company proposes to grant rights to purchase shares of Common Stock to eligible employees of the Company and its Participating Corporations pursuant to this Plan. The Company intends this Plan to qualify as an "employee stock purchase plan" under Section 423 of the Code (including any amendments to or replacements of such Section), and this Plan shall be so construed, although the Company makes no undertaking or representation to maintain such qualification. Any term not expressly defined in this Plan but defined in Section 423 of the Code shall have the definition provided by Section 423 of the Code. In addition, with regard to offers of options to purchase shares of Common Stock under the Plan to employees working for a Subsidiary or an Affiliate outside the United States, this Plan authorizes the grant of options under a Non-Section 423 Component that is not intended to meet the requirements of Section 423 of the Code provided that, to the extent necessary under Section 423 of the Code, the other terms and conditions of this Plan are met.

Subject to Section 14, a total of 165,000 shares of Common Stock is reserved for issuance under this Plan. In addition, on each January 1 for each of the calendar years beginning 2019 and ending 2026, the aggregate number of shares of Common Stock reserved for issuance under the Plan shall be increased automatically by the number of shares equal to one percent (1%) of the total number of outstanding shares of Common Stock and Common Stock equivalents outstanding on the immediately preceding December 31 (rounded down to the nearest whole share); provided, that the Board may in its sole discretion reduce the amount of the increase in any particular year. Subject to Section 14, no more than 2,900,000 shares of Common Stock may be issued over the term of this Plan. The number of shares initially reserved for issuance under this Plan and the maximum number of shares that may be issued under this Plan shall be subject to adjustments effected in accordance with Section 14. Any or all such shares may be granted under the Section 423 Component.

3. ADMINISTRATION. The Plan will be administered by the Committee. Subject to the provisions of this Plan and the limitations of Section 423 of the Code or any successor provision in the Code, all questions of interpretation or application of this Plan shall be determined by the Committee and its decisions shall be final and binding upon all eligible employees and Participants. The Committee will have full and exclusive discretionary authority to construe, interpret and apply the terms of this Plan, to determine eligibility, to designate the Participating Corporations, to determine whether Participating Corporations shall participate in the Section 423 Component or Non-Section 423 Component and to decide upon any and all claims filed under the Plan. Every finding, decision and determination made by the Committee will, to the full extent permitted by law, be final and binding upon all parties. Notwithstanding any provision to the contrary in this Plan, the Committee may adopt rules, sub-plans, and/or procedures relating to the operation and administration of this Plan designed to comply with local laws, regulations or customs or to achieve tax, securities law or other objectives for eligible employees outside of the United States. The Committee will have the authority to determine the Fair Market Value of the Common Stock (which determination shall be final, binding and conclusive for all purposes) in accordance with Section 8 below and to interpret Section 8 of this Plan in connection with circumstances that impact the Fair Market Value. Members of the Committee shall receive no compensation for their services in connection with the administration of this Plan, other than standard fees as established from time to time by the Board for services rendered by Board members serving on Board committees. All expenses incurred in connection with the administration of this Plan shall be paid by the Company. For purposes of this Plan, the Committee may designate separate offerings under the Plan (the terms of which need not be identical) in which eligible employees of one or more Participating Corporations will participate, even if the dates of the applicable Offering Periods of each such offering are identical.

4. ELIGIBILITY.

(a) Any employee of the Company or the Participating Corporations is eligible to participate in an Offering Period under this Plan, except that one or more of the following categories of employees may be excluded from eligibility under this Plan by the Committee (other than where such exclusion is prohibited by applicable law):

(i) (employees who are customarily employed for twenty (20) hours or less per week;

(ii) employees who are customarily employed for five (5) months or less in a calendar year; and

(iii) employees who do not meet any other eligibility requirements that the Committee may choose to impose (within the limits permitted by the Code).

Notwithstanding the foregoing, an individual shall not be eligible if his or her participation in this Plan is prohibited by the law of any country having jurisdiction over him or her, if complying with the laws of the applicable country would cause the Plan to violate Section 423 of the Code, or if he or she is subject to a collective bargaining agreement that does not provide for participation in this Plan.

(b) No employee who, together with any other person whose stock would be attributed to such employee pursuant to Section 424(d) of the Code, owns stock or holds options to purchase stock possessing five percent (5%) or more of the total combined voting power or value of all classes of stock of the Company or its Parent or Subsidiary or who, as a result of being granted an option under this Plan with respect to such Offering Period, would own stock or hold options to purchase stock possessing five percent (5%) or more of the total combined voting power or value of all classes of stock of the Company or its Parent or Subsidiary shall be granted an option to purchase Common Stock under this Plan. Notwithstanding the foregoing, the rules of Section 424(d) of the Code shall apply in determining share ownership and the extent to which shares held under outstanding equity awards are to be treated as owned by the employee.

5. OFFERING DATES.

(a) Each Offering Period of this Plan may be of up to twenty-seven (27) months' duration and shall commence and end at the times designated by the Committee. Each Offering Period shall consist of one Purchase Period during which Contributions made by Participants are accumulated under this Plan.

(b) The initial Offering Period shall commence on the Effective Date and shall end with the Purchase Date that occurs on August 15, 2016 or another date selected by the Committee which is approximately six (6) months after the commencement of the initial Offering Period, but no more than twenty-seven (27) months after the commencement of the initial Offering period. The initial Offering Period shall consist of one Purchase Period. Thereafter, a six-month Offering Period shall commence on each February 16 and August 16, with each such Offering Period also consisting of one six-month Purchase Period, except as otherwise provided by an applicable sub-plan, or on such other date determined by the Committee. The Committee may at any time establish a different duration for an Offering Period or Purchase Period to be effective after the next scheduled Purchase Date, up to a maximum duration of twenty-seven (27) months.

(c) To the extent applicable, if the Fair Market Value on the first day of the current Offering Period in which a Participant is enrolled is higher than the Fair Market Value on the first day of any subsequent Purchase Period, the current Offering Period shall end, and Participant shall be automatically enrolled in the subsequent Offering Period, as specified under Section 5(a) or Section 5(b), as applicable. Any funds accumulated in a Participant' s account prior to the first day of such subsequent Offering Period will be applied to the purchase of shares on the Purchase Date immediately prior to the first day of such subsequent Offering Period, if any.

6. PARTICIPATION IN THIS PLAN.

(a) Any employee who is an eligible employee determined in accordance with Section 4 immediately prior to the initial Offering Period will be automatically enrolled in the initial Offering Period under this Plan for the maximum number of shares of Common Stock purchasable. With respect to subsequent Offering Periods, any eligible employee determined in accordance with Section 4 will be

eligible to participate in this Plan, subject to the requirement of Section 6(b) hereof and the other terms and provisions of this Plan.

(b) With respect to Offering Periods after the initial Offering Period, a Participant may elect to participate in this Plan by submitting an enrollment agreement prior to the commencement of the Offering Period (or such earlier date as the Committee may determine) to which such agreement relates.

(c) Once an employee becomes a Participant in an Offering Period, then such Participant will automatically participate in each subsequent Offering Period commencing immediately following the last day of the prior Offering Period unless the Participant withdraws or is deemed to withdraw from this Plan or terminates further participation in an Offering Period as set forth in Section 11 below. A Participant who is continuing participation pursuant to the preceding sentence is not required to file any additional enrollment agreement in order to continue participation in this Plan; a Participant who is not continuing participation pursuant to the preceding sentence is required to file an enrollment agreement prior to the commencement of the Offering Period (or such earlier date as the Committee may determine) to which such agreement relates.

7. GRANT OF OPTION ON ENROLLMENT. Becoming a Participant with respect to an Offering Period will constitute the grant (as of the Offering Date) by the Company to such Participant of an option to purchase on the Purchase Date up to that number of shares of Common Stock of the Company determined by a fraction, the numerator of which is the amount accumulated in such Participant's Contribution account during such Purchase Period and the denominator of which is the lower of (i) eighty-five percent (85%) of the Fair Market Value of a share of Common Stock on the Offering Date (but in no event less than the par value of a share of the Common Stock), or (ii) eighty-five percent (85%) of the Fair Market Value of a share of the Common Stock on the Purchase Date; provided, however, that for the Purchase Period within the initial Offering Period the numerator shall be fifteen percent (15%) of the Participant's compensation for such Purchase Period, or such lower percentage as determined by the Committee prior to the start of the Offering Period, and provided, further, that the number of shares of Common Stock subject to any option granted pursuant to this Plan shall not exceed the lesser of (x) the maximum number of shares set by the Committee pursuant to Section l0(b) below with respect to the applicable Purchase Date, or (y) the maximum number of shares which may be purchased pursuant to Section 10(a) below with respect to the applicable Purchase Date.

8. PURCHASE PRICE. The Purchase Price per share at which a share of Common Stock will be sold in any Offering Period shall be eighty-five percent (85%) of the lesser of:

(a) The Fair Market Value on the Offering Date; or

(b) The Fair Market Value on the Purchase Date.

9. PAYMENT OF PURCHASE PRICE; CONTRIBUTION CHANGES; SHARE ISSUANCES.

(a) The Purchase Price shall be accumulated by regular payroll deductions made during each Offering Period, unless the Committee determines with respect to categories of Participants outside the United States that Contributions may be made in another form due to local legal requirements. The Contributions are made as a percentage of the Participant's Compensation in one percent (1%) increments not less than one percent (1%), nor greater than fifteen percent (15%) or such lower limit set by the Committee. ***"Compensation"*** shall mean base salary (or in foreign jurisdictions, equivalent cash compensation); however, the Committee may at any time prior to the beginning of an Offering Period determine that for that and future Offering Periods, Compensation shall mean all cash compensation reported on the employee's Form W-2 or corresponding local country tax return, including without limitation base salary or regular hourly wages , bonuses, incentive compensation, commissions, overtime, shift premiums, and draws against commissions. For purposes of determining a Participant's Compensation, any election by such Participant to reduce his or her regular cash remuneration under Sections 125 or 40l(k) of the Code (or in foreign jurisdictions, equivalent salary deductions) shall be treated as if the Participant did not make such election. Contributions shall commence on the first payday following the last Purchase Date (with respect to the initial Offering Period, as soon as practicable following the effective date of filing with the U.S. Securities and Exchange Commission a securities registration statement for the Plan) and shall continue to the end of the Offering Period unless sooner altered or terminated as provided in this Plan. Notwithstanding the foregoing, the terms of any sub-plan may permit matching shares without the payment of any purchase price.

(b) A Participant may decrease the rate of Contributions during an Offering Period by filing with the Company or a third party designated by the Company a new authorization for Contributions, with the new rate to become effective no later than the second payroll period commencing after the Company's receipt of the authorization and continuing for the remainder of the Offering Period unless changed as described below. A decrease in the rate of Contributions may be made once during an Offering Period, but up to twice during the initial Offering Period, or more frequently under rules determined by the Committee. A Participant may increase or decrease the rate of Contributions for any subsequent Offering Period by filing with the Company or a third party designated by the Company a new authorization for Contributions prior to the beginning of such Offering Period, or such other time period as specified by the Committee.

(c) A Participant may reduce his or her Contribution percentage to zero during an Offering Period by filing with the Company or a third party designated by the Company a request for cessation of Contributions. Such reduction shall be effective beginning no later than the second payroll period after the Company' s receipt of the request and no further Contributions will be made for the duration of the Offering Period. Contributions credited to the Participant's account prior to the effective date of the request shall be used to purchase shares of Common Stock in accordance with Subsection (e) below. A reduction of the Contribution percentage to zero shall be treated as such Participant' s withdrawal from such Offering Period and the Plan, effective as of the day after the next Purchase Date following the filing date of such request with the Company.

(d) All Contributions made for a Participant are credited to his or her book account under this Plan and are deposited with the general funds of the Company, except to the extent local legal restrictions outside the United States require segregation of such Contributions. No interest accrues on the Contributions, except to the extent required due to local legal requirements. All Contributions received or held by the Company may be used by the Company for any corporate purpose, and the Company shall not be obligated to segregate such Contributions, except to the extent necessary to comply with local legal requirements outside the United States.

(e) On each Purchase Date, so long as this Plan remains in effect and provided that the Participant has not submitted a signed and completed withdrawal form before that date which notifies the Company that the Participant wishes to withdraw from that Offering Period under this Plan and have all Contributions accumulated in the account maintained on behalf of the Participant as of that date returned to the Participant, the Company shall apply the funds then in the Participant's account to the purchase of whole shares of Common Stock reserved under the option granted to such Participant with respect to the Offering Period to the extent that such option is exercisable on the Purchase Date. The Purchase Price per share for such automatic purchase shall be as specified in Section 8 of this Plan. Any fractional share, as calculated under this Subsection (e), shall be rounded down to the next lower whole share, unless the Committee determines with respect to all Participants that any fractional share shall be credited as a fractional share. Any amount remaining in a Participant's account on a Purchase Date that is less than the amount necessary to purchase a full share of Common Stock shall be returned to the Participant, without interest (except to the extent necessary to comply with local legal requirements outside the United States); however, the Committee may provide that such amounts may be carried forward into the next Purchase Period or Offering Period, as the case may be. In the event that this Plan has been oversubscribed, all funds not used to purchase shares on the Purchase Date shall be returned to the Participant, without interest (except to the extent required due to local legal requirements outside the United States). No Common Stock shall be purchased on a Purchase Date on behalf of any employee whose participation in this Plan has terminated prior to such Purchase Date, except to the extent required due to local legal requirements outside the United States.

(f) As promptly as practicable after the Purchase Date, the Company shall issue shares for the Participant's benefit representing the shares purchased upon exercise of his or her option to purchase shares hereunder.

(g) During a Participant's lifetime, his or her option to purchase shares hereunder is exercisable only by him or her. The Participant will have no interest or voting right in shares covered by his or her option until such option has been exercised.

(h) To the extent required by applicable federal, state, local or foreign law, a Participant shall make arrangements satisfactory to the Company and the Participating Corporation employing the Participant for the satisfaction of any withholding tax obligations that arise in connection with the Plan. The Company or any Subsidiary or Affiliate, as applicable, may withhold, by any method permissible under the applicable law, the amount necessary for the Company or Subsidiary or Affiliate, as applicable,

to meet applicable withholding obligations, including any withholding required to make available to the Company or Subsidiary or Affiliate, as applicable, any tax deductions or benefits attributable to the sale or early disposition of shares of Common Stock by a Participant. The Company shall not be required to issue any shares of Common Stock under the Plan until such obligations are satisfied.

10. LIMITATIONS ON SHARES TO BE PURCHASED.

(a) Any other provision of the Plan notwithstanding, no Participant shall purchase Common Stock with a Fair Market Value in excess of the following limit:

(i) In the case of Common Stock purchased during an Offering Period that commenced in the current calendar year, the limit shall be equal to (A) $25,000 minus (B) the Fair Market Value of the Common Stock that the Participant previously purchased in the current calendar year (under this Plan and all other employee stock purchase plans of the Company or any Parent or Subsidiary).

(ii) In the case of Common Stock purchased during an Offering Period that commenced in the immediately preceding calendar year, the limit shall be equal to (A) $50,000 minus (B) the Fair Market Value of the Common Stock that the Participant previously purchased (under this Plan and all other employee stock purchase plans of the Company or any Parent or Subsidiary) in the current calendar year and in the immediately preceding calendar year.

For purposes of this Subsection (a), the Fair Market Value of Common Stock shall be determined in each case as of the beginning of the Offering Period in which such Common Stock is purchased. Employee stock purchase plans not described in Section 423 of the Code shall be disregarded. If a Participant is precluded by this Subsection (a) from purchasing additional Common Stock under the Plan, then his or her Contributions shall automatically be discontinued and shall automatically resume at the beginning of the earliest Purchase Period that will end in the next calendar year (if he or she then is an eligible employee), provided that when the Company automatically resumes such Contributions, the Company must apply the rate in effect immediately prior to such suspension.

(b) The Committee shall establish a maximum number of shares that may be purchased on any one Purchase Date. The Committee will communicate the applicable limit to Participants prior to commencement of the Offering Period for which it is effective.

(c) If the number of shares to be purchased on a Purchase Date by all Participants exceeds the number of shares then available for issuance under this Plan, then the Company will make a pro rata allocation of the remaining shares in as uniform a manner as shall be reasonably practicable and as the Committee shall determine to be equitable. In such event, the Company will give notice of such reduction of the number of shares to be purchased under a Participant' s option to each Participant affected.

(d) Any Contributions accumulated in a Participant' s account that are not used to purchase stock due to the limitations in this Section 10, and not subject to the automatic purchase provision of Section 9(e), shall be returned to the Participant as soon as practicable after the end of the applicable Purchase Period, without interest (except to the extent required due to local legal requirements outside the United States).

11. WITHDRAWAL.

(a) Each Participant may withdraw from an Offering Period under this Plan pursuant to a method specified for such purpose by the Company. Such withdrawal may be elected at any time prior to the end of an Offering Period, or such other time period as specified by the Committee.

(b) Upon withdrawal from this Plan, the accumulated Contributions shall be returned to the withdrawn Participant, without interest (except to the extent required due to local legal requirements outside the United States), and his or her interest in this Plan shall terminate. In the event a Participant voluntarily elects to withdraw from this Plan, he or she may not resume his or her participation in this Plan during the same Offering Period, but he or she may participate in any Offering Period under this Plan which commences on a date subsequent to such withdrawal by filing a new authorization for Contributions in the same manner as set forth in Section 6 above for initial participation in this Plan.

12. TERMINATION OF EMPLOYMENT. Termination of a Participant's employment for any reason, including retirement, death, disability, or the failure of a Participant to remain an eligible employee

of the Company or of a Participating Corporation, immediately terminates his or her participation in this Plan (except as required due to local legal requirements outside the United States). In such event, accumulated Contributions credited to the Participant's account will be returned to him or her or, in the case of his or her death, to his or her legal representative, without interest (except to the extent required due to local legal requirements outside the United States). For purposes of this Section 12, an employee will not be deemed to have terminated employment or failed to remain in the continuous employ of the Company or of a Participating Corporation in the case of sick leave, military leave, or any other leave of absence approved by the Company; provided that such leave is for a period of not more than ninety (90) days or reemployment upon the expiration of such leave is guaranteed by contract or statute. The Company will have sole discretion to determine whether a Participant has terminated employment and the effective date on which the Participant terminated employment, regardless of any notice period or garden leave required under local law.

13. RETURN OF CONTRIBUTIONS. In the event a Participant's interest in this Plan is terminated by withdrawal, termination of employment or otherwise, or in the event this Plan is terminated by the Board, the Company shall deliver to the Participant all accumulated Contributions credited to such Participant's account. No interest shall accrue on the Contributions of a Participant in this Plan (except to the extent required due to local legal requirements outside the United States).

14. CAPITAL CHANGES. If the number of outstanding shares is changed by a stock dividend, recapitalization, stock split, reverse stock split, subdivision, combination, reclassification or similar change in the capital structure of the Company, without consideration, then the Committee shall adjust the number and class of Common Stock that may be delivered under the Plan, the Purchase Price per share and the number of shares of Common Stock covered by each option under the Plan which has not yet been exercised, and the numerical limits of Sections 2 and 10 shall be proportionately adjusted, subject to any required action by the Board or the stockholders of the Company and in compliance with the applicable securities laws; provided that fractions of a share will not be issued.

15. NONASSIGNABILITY. Neither Contributions credited to a Participant's account nor any rights with regard to the exercise of an option or to receive shares under this Plan may be assigned, transferred, pledged or otherwise disposed of in any way (other than by will, the laws of descent and distribution or as provided in Section 22 below) by the Participant. Any such attempt at assignment, transfer, pledge or other disposition shall be void and without effect.

16. USE OF PARTICIPANT FUNDS AND REPORTS. The Company may use all Contributions received or held by it under the Plan for any corporate purpose, and the Company will not be required to segregate Participant Contributions (except to the extent required due to local legal requirements outside the United States). Until shares are issued, Participants will only have the rights of an unsecured creditor unless otherwise required under local law. Each Participant shall receive promptly after the end of each Purchase Period a report of his or her account setting forth the total Contributions accumulated, the number of shares purchased, the per share price thereof and the remaining cash balance, if any, carried forward to the next Purchase Period or Offering Period, as the case may be.

17. NOTICE OF DISPOSITION. Each U.S. taxpayer Participant shall notify the Company in writing if the Participant disposes of any of the shares purchased in any Offering Period pursuant to this Plan if such disposition occurs within two (2) years from the Offering Date or within one (1) year from the Purchase Date on which such shares were purchased (the ***"Notice Period).*** The Company may, at any time during the Notice Period, place a legend or legends on any certificate representing shares acquired pursuant to this Plan requesting the Company's transfer agent to notify the Company of any transfer of the shares. The obligation of the Participant to provide such notice shall continue notwithstanding the placement of any such legend on the certificates.

18. NO RIGHTS TO CONTINUED EMPLOYMENT. Neither this Plan nor the grant of any option hereunder shall confer any right on any employee to remain in the employ of the Company or any Participating Corporation, or restrict the right of the Company or any Participating Corporation to terminate such employee ' s employment.

19. EQUAL RIGHTS AND PRIVILEGES. All eligible employees granted an option under the Section 423 Component of this Plan shall have equal rights and privileges with respect to this Plan or within any separate offering under the Plan so that this Plan qualifies as an "employee stock purchase plan" within the meaning of Section 423 or any successor provision of the Code and the related regulations. Any provision of this Plan which is inconsistent with Section 423 or any successor provision of the Code, without further act or amendment by the Company, the Committee or the Board, shall be

reformed to comply with the requirements of Section 423. This Section 19 shall take precedence over all other provisions in this Plan.

20. NOTICES. All notices or other communications by a Participant to the Company under or in connection with this Plan shall be deemed to have been duly given when received in the form specified by the Company at the location, or by the person, designated by the Company for the receipt thereof.

21. TERM; STOCKHOLDER APPROVAL. The amendment and restatement of the Plan shall be approved by the stockholders of the Company, in any manner permitted by applicable corporate law, within twelve (12) months before or after the date this amendment and restatement of the Plan is adopted by the Board. The amendment and restatement of the Plan will become effective upon approval by stockholders at the 2018 Annual Meeting of Stockholders. No purchase of shares that are subject to such stockholder approval before becoming available under this Plan shall occur prior to stockholder approval of such shares and the Board or Committee may delay any Purchase Date and postpone the commencement of any Offering Period subsequent to such Purchase Date as deemed necessary or desirable to obtain such approval (provided that if a Purchase Date would occur more than twenty-seven (27) months after commencement of the Offering Period to which it relates, then such Purchase Date shall not occur and instead such Offering Period shall terminate without the purchase of such shares and Participants in such Offering Period shall be refunded their Contributions without interest). If the amendment and restatement of the Plan is not approved by the stockholders of the Company within twelve (12) months before or after the date this amendment and restatement of the Plan is adopted by the Board, then it shall be null and void and the Plan shall continue in effect without the terms approved in the amendment and restatement. This Plan shall continue until the earlier to occur of (a) termination of this Plan by the Board (which termination may be effected by the Board at any time pursuant to Section 25 below), (b) issuance of all of the shares of Common Stock reserved for issuance under this Plan, or (c) the tenth anniversary of the Effective Date under the Plan.

22. DESIGNATION OF BENEFICIARY.

(a) Unless otherwise determined by the Committee, a Participant may file a written designation of a beneficiary who is to receive any cash from the Participant's account under this Plan in the event of such Participant's death prior to a Purchase Date. Such form shall be valid only if it was filed with the Company at the prescribed location before the Participant's death.

(b) If authorized by the Company, such designation of beneficiary may be changed by the Participant at any time by written notice filed with the Company at the prescribed location before the Participant's death. In the event of the death of a Participant and in the absence of a beneficiary validly designated under this Plan who is living at the time of such Participant' s death, the Company shall deliver such cash to the executor or administrator of the estate of the Participant or to the legal heirs of the Participant.

23. CONDITIONS UPON ISSUANCE OF SHARES; LIMITATION ON SALE OF SHARES. Shares shall not be issued with respect to an option unless the exercise of such option and the issuance and delivery of such shares pursuant thereto shall comply with all applicable provisions of law, domestic or foreign, including, without limitation, the U.S. Securities Act of 1933, as amended, the U.S. Securities Exchange Act of 1934, as amended, the rules and regulations promulgated thereunder, and the requirements of any stock exchange or automated quotation system upon which the shares may then be listed, exchange control restrictions and/or securities law restrictions outside the United States, and shall be further subject to the approval of counsel for the Company with respect to such compliance. Shares may be held in trust or subject to further restrictions as permitted by any subplan.

24. APPLICABLE LAW. The Plan shall be governed by the substantive laws (excluding the conflict of laws rules) of the State of Delaware.

25. AMENDMENT OR TERMINATION. The Committee, in its sole discretion, may amend, suspend, or terminate the Plan, or any part thereof, at any time and for any reason. Unless otherwise required by applicable law, if the Plan is terminated, the Committee, in its discretion, may elect to terminate all outstanding Offering Periods either immediately or upon completion of the purchase of shares of Common Stock on the next Purchase Date (which may be sooner than originally scheduled, if determined by the Committee in its discretion), or may elect to permit Offering Periods to expire in accordance with their terms (and subject to any adjustment pursuant to Section 14). If an Offering Period is terminated prior to its previously-scheduled expiration, all amounts then credited to Participants'

accounts for such Offering Period, which have not been used to purchase shares of Common Stock, shall be returned to those Participants (without interest thereon, except as otherwise required under local laws) as soon as administratively practicable. Further, the Committee will be entitled to change the Purchase Periods and Offering Periods, limit the frequency and/or number of changes in the amount contributed during an Offering Period, establish the exchange ratio applicable to amounts contributed in a currency other than U.S. dollars, permit payroll withholding in excess of the amount designated by a Participant in order to adjust for delays or mistakes in the administration of the Plan, establish reasonable waiting and adjustment periods and/or accounting and crediting procedures to ensure that amounts applied toward the purchase of Common Stock for each Participant properly correspond with amounts contributed from the Participant' s base salary and other eligible compensation, and establish such other limitations or procedures as the Committee determines in its sole discretion advisable which are consistent with the Plan. Such actions will not require stockholder approval or the consent of any Participants. However, no amendment shall be made without approval of the stockholders of the Company (obtained in accordance with Section 21 above) within twelve (12) months of the adoption of such amendment (or earlier if required by Section 21) if such amendment would: (a) increase the number of shares that may be issued under this Plan; or (b) change the designation of the employees (or class of employees) eligible for participation in this Plan. In addition, in the event the Board or Committee determines that the ongoing operation of the Plan may result in unfavorable financial accounting consequences, the Board or Committee may, in its discretion and, to the extent necessary or desirable, modify, amend or terminate the Plan to reduce or eliminate such accounting consequences including, but not limited to: (i) amending the definition of compensation, including with respect to an Offering Period underway at the time; (ii) altering the Purchase Price for any Offering Period including an Offering Period underway at the time of the change in Purchase Price; (iii) shortening any Offering Period by setting a Purchase Date, including an Offering Period underway at the time of the Committee' s action; (iv) reducing the maximum percentage of Compensation a participant may elect to set aside as Contributions; and (v) reducing the maximum number of shares a Participant may purchase during any Offering Period. Such modifications or amendments will not require approval of the stockholders of the Company or the consent of any Participants.

26. CORPORATE TRANSACTIONS. In the event of a Corporate Transaction, the Offering Period for each outstanding right to purchase Common Stock will be shortened by setting a new Purchase Date and will end on the new Purchase Date. The new Purchase Date shall occur on or prior to the consummation of the Corporate Transaction, as determined by the Board or Committee, and the Plan shall terminate on the consummation of the Corporate Transaction.

27. CODE SECTION 409A; TAX QUALIFICATION.

(a) Options granted under the Plan generally are exempt from the application of Section 409A of the Code. However, options granted to U.S. taxpayers which are not intended to meet the Code Section 423 requirements are intended to be exempt from the application of Section 409A of the Code under the short-term deferral exception and any ambiguities shall be construed and interpreted in accordance with such intent. Subject to Subsection (b), options granted to U.S. taxpayers outside of the Code Section 423 requirements shall be subject to such terms and conditions that will permit such options to satisfy the requirements of the short-term deferral exception available under Section 409A of the Code, including the requirement that the shares of Common Stock subject to an option be delivered within the short-term deferral period. Subject to Subsection (b), in the case of a Participant who would otherwise be subject to Section 409A of the Code, to the extent the Committee determines that an option or the exercise, payment, settlement or deferral thereof is subject to Section 409A of the Code, the option shall be granted, exercised, paid, settled or deferred in a manner that will comply with Section 409A of the Code, including Treasury regulations and other interpretive guidance issued thereunder, including without limitation any such regulations or other guidance that may be issued after the Effective Date. Notwithstanding the foregoing, the Company shall have no liability to a Participant or any other party if the option that is intended to be exempt from or compliant with Section 409A of the Code is not so exempt or compliant or for any action taken by the Committee with respect thereto.

(b) Although the Company may endeavor to (i) qualify an option for favorable tax treatment under the laws of the United States or jurisdictions outside of the United States or (ii) avoid adverse tax treatment (e.g., under Section 409A of the Code), the Company makes no representation to that effect and expressly disavows any covenant to maintain favorable or avoid unfavorable tax treatment, notwithstanding anything to the contrary in this Plan, including Subsection (a). The Company shall be unconstrained in its corporate activities without regard to the potential negative tax impact on Participants under the Plan.

28. DEFINITIONS.

(a) ***"Affiliate"*** means any entity, other than a Subsidiary or Parent, (i) that, directly or indirectly, is controlled by, controls or is under common control with, the Company and (ii) in which the Company has a significant equity interest, in either case as determined by the Committee, whether now or hereafter existing.

(b) ***"Board"*** shall mean the Board of Directors of the Company.

(c) ***"Code"*** shall mean the U.S. Internal Revenue Code of 1986, as amended.

(d) ***"Committee"*** shall mean the Compensation Committee of the Board that consists exclusively of one or more members of the Board appointed by the Board.

(e) ***"Common Stock"*** shall mean the common stock of the Company.

(f) ***"Company"*** shall mean Spyre Therapeutics, Inc. (f/k/a Aeglea BioTherapeutics, Inc.).

(g) ***"Contributions"*** means payroll deductions taken from a Participant's Compensation and used to purchase shares of Common Stock under the Plan and, to the extent payroll deductions are not permitted by applicable laws (as determined by the Committee in its sole discretion) contributions by other means, provided, however, that allowing such other contributions does not jeopardize the qualification of the Plan as an "employee stock purchase plan" under Section 423 of the Plan.

(h) ***"Corporate Transaction"*** means the occurrence of any of the following events: (i) any "person" (as such term is used in Sections 13(d) and 14(d) of the Exchange Act) becomes the "beneficial owner" (as defined in Rule 13d-3 of the Exchange Act), directly or indirectly, of securities of the Company representing fifty percent (50%) or more of the total voting power represented by the Company's then outstanding voting securities; or (ii) the consummation of the sale or disposition by the Company of all or substantially all of the Company's assets; or (iii) the consummation of a merger or consolidation of the Company with any other corporation, other than a merger or consolidation which would result in the voting securities of the Company outstanding immediately prior thereto continuing to represent (either by remaining outstanding or by being converted into voting securities of the surviving entity or its parent) at least fifty percent (50%) of the total voting power represented by the voting securities of the Company or such surviving entity or its parent outstanding immediately after such merger or consolidation.

(i) ***"Effective Date"*** shall mean the date on which the Registration Statement covering the initial public offering of the shares of Common Stock is declared effective by the U.S. Securities and Exchange Commission.

(j) ***"Fair Market Value"*** shall mean, as of any date, the value of a share of Common Stock determined as follows:

(1) if such Common Stock is then quoted on the Nasdaq Global Select Market, the Nasdaq Global Market or the Nasdaq Capital Market (collectively, the ***"Nasdaq Market"),*** its closing price on the Nasdaq Market on the date of determination, or if there are no sales for such date, then the last preceding business day on which there were sales, as reported in *The Wall Street Journal* or such other source as the Board or the Committee deems reliable; or

(2) if such Common Stock is publicly traded and is then listed on a national securities exchange, its closing price on the date of determination on the principal national securities exchange on which the Common Stock is listed or admitted to trading as reported in *The Wall Street Journal* or such other source as the Board or the Committee deems reliable; or

(3) if such Common Stock is publicly traded but is neither quoted on the Nasdaq Market nor listed or admitted to trading on a national securities exchange, the average of the closing bid and asked prices on the date of determination as reported in *The Wall Street Journal* or such other source as the Board or the Committee deems reliable; or

(4) with respect to the initial Offering Period, Fair Market Value on the Offering Date shall be the price at which shares of Common Stock are offered to the public pursuant to the Registration Statement covering the initial public offering of shares of Common Stock; or

(5) if none of the foregoing is applicable, by the Board or the Committee in good faith.

(k) ***"IPO"*** shall mean the initial public offering of Common Stock.

(l) ***"Non-Section 423 Component"*** means the part of the Plan which is not intended to meet the requirements set forth in Section 423 of the Code.

(m) ***"Notice Period"*** shall mean within two (2) years from the Offering Date or within one (1) year from the Purchase Date on which such shares were purchased.

(n) ***"Offering Date"*** shall mean the first business day of each Offering Period. However, for the initial Offering Period the Offering Date shall be the Effective Date.

(o) ***"Offering Period"*** shall mean a period with respect to which the right to purchase Common Stock may be granted under the Plan, as determined by the Committee pursuant to Section 5(a).

(p) ***"Parent"*** shall have the same meaning as " parent corporation" in Sections 424(e) and 424(±) of the Code.

(q) ***"Participant"*** shall mean an eligible employee who meets the eligibility requirements set forth in Section 4 and who is either automatically enrolled in the initial Offering Period or who elects to participate in this Plan pursuant to Section 6(b).

(r) ***"Participating Corporation"*** shall mean any Parent, Subsidiary or Affiliate that the Committee designates from time to time as eligible to participate in this Plan. For purposes of the Section 423 Component, only the Parent and Subsidiaries may be Participating Corporations, provided, however, that at any given time a Parent or Subsidiary that is a Participating Corporation under the Section 423 Component shall not be a Participating Corporation under the Non-Section 423 Component.

The Committee may provide that any Participating Corporation shall only be eligible to participate in the Non-Section 423 Component.

(s) ***"Plan"*** shall mean this Spyre Therapeutics, Inc. 2016 Employee Stock Purchase Plan, as may be amended from time to time.

(t) ***"Purchase Date"*** shall mean the last business day of each Purchase Period.

(u) ***"Purchase Period"*** shall mean a period during which Contributions may be made toward the purchase of Common Stock under the Plan, as determined by the Committee pursuant to Section 8.

(v) ***"Purchase Price"*** shall mean the price at which Participants may purchase shares of Common Stock under the Plan, as determined pursuant to Section 8.

(w) ***"Section 423 Component"*** means the part of the Plan, which excludes the Non- Section 423 Component, pursuant to which options to purchase shares of Common Stock under the Plan that satisfy the requirements for "employee stock purchase plans" set forth in Section 423 of the Code may be granted to eligible employees.

(x) ***"Subsidiary"*** shall have the same meaning as "subsidiary corporation" in Sections 424(e) and 424(f) of the Code.

Exhibit 10.19

August 18, 2023

Heidy King-Jones

Re: Offer of Employment

Dear Heidy:

On behalf of Aeglea BioTherapeutics, Inc. (the "Company"), I am very pleased to offer you a position as Chief Legal Officer and Corporate Secretary (the "Role") pursuant to this letter agreement (the "Agreement"), provided you accept such offer as indicated by your signature below.

Your employment with the Company in the Role will commence as of September 1, 2023 or other date mutually agreed between you and the Company in writing (the "Effective Date"). Should you not commence services by the Effective Date or if this Agreement is otherwise terminated on or prior to the Effective Date, you hereby agree that this Agreement shall be void *ab initio* and of no force or effect, other than as described herein.

1. Position. While serving in the Role, you will initially report to Cameron Turtle as the Company's Chief Operating Officer, and upon his promotion to Chief Executive Officer, you shall report to the Company's Chief Executive Officer. You will have such duties, authorities, and responsibilities as are customarily associated with the Role. This is a full-time employment position. It is understood and agreed that, commencing as of the Effective Date you will not engage in any other employment, consulting or other business activities (whether full-time or part-time), except as expressly authorized in writing by the Company. Notwithstanding the foregoing, you may engage in religious, charitable and other community activities so long as such activities do not unreasonably interfere or conflict with your obligations to the Company.

2. Base Salary. Upon and following the Effective Date, as cash compensation for your services, the Company will pay you an initial base salary of $470,000 per year, payable in accordance with the Company's standard payroll schedule and subject to applicable deductions and withholdings. Your base salary will be subject to periodic review and potential adjustment in the Company's discretion. Your base salary in effect at any given time is referred to herein as the "Base Salary."

3. Annual Bonus. Commencing as of the Effective Date, you will be eligible to receive an annual performance bonus targeted at 40% of your Base Salary. The target annual bonus in effect at any given time is referred to herein as "Target Bonus." Your 2023 annual bonus will be prorated based on your period of employment following the Effective Date. The actual bonus amount is discretionary and may be subject to achievement of performance targets established by the Company for such year. To earn an annual bonus, you must be (except as otherwise provided herein) employed by the Company as of the payment date of such bonus. Any annual bonus will be paid no later than March 15th of the calendar year following the calendar year to which such bonus relates.

4. Inducement Grant. Subject to approval by the Company's Board and as a material inducement to you agreeing to become employed by the Company, as soon as practicable following the Effective Date, the Company will grant you nonqualified stock options to purchase a number of shares of the Company's common stock equal to 1.00% of the total outstanding shares of the Company's common stock as of the Effective Date with an exercise price equal to the fair market value of the underlying shares on the date of grant as determined by the Board (the "Inducement Options"). The Inducement Options will vest over a four-year period following your grant date, with

25% of the Inducement Options vesting on the first anniversary of your grant date, and the remainder vesting in 36 equal monthly installments on each monthly anniversary thereafter, in each case, subject to your continued services with the Company through the applicable vesting dates. The Inducement Options will be governed by the terms of the related award agreement, the Company's 2018 Equity Inducement Plan and the terms and conditions approved by the Board. The Inducement Options will be granted in compliance with NASDAQ Listing Rule 5635(c)(4) as a material inducement to you entering into employment with the Company.

5. Benefits/Paid Time Off. Commencing as of the Effective Date, you will be eligible, subject to the terms of the applicable plans and programs, to participate in the employee benefits and insurance programs generally made available to the Company's full-time employees. Details of such benefits programs, including applicable employee contributions and waiting periods, if applicable, will be made available to you when such benefit(s) become available. You will be entitled to paid time off consistent with the terms of the Company's paid time off policy, as in effect from time to time. The Company reserves the right to modify, limit, amend or cancel any of its benefits plans or programs at any time.

6. Expense Reimbursement. The Company will reimburse you for all reasonable and necessary expenses incurred by you in connection with performing your duties as an employee of the Company and that are pre-approved by the Company, provided that you comply with any Company policy or practice on submitting, accounting for and documenting such expenses.

7. Location. Your primary work location will be remotely in Massachusetts, provided that you may be required to engage in reasonable travel for business, consistent with the Company's business needs. You may change your remote work location with prior written notice to and approval from the Company.

8. At-Will Employment; Date of Termination. At all times, your employment with the Company is "at will," meaning you or the Company may terminate it at any time for any or no reason, subject to the terms of this Agreement. Although your job duties, title, reporting structure, compensation and benefits, as well as the Company's benefit plans and personnel policies and procedures, may change from time to time (subject to the terms of this Agreement), the "at will" nature of your employment may only be changed in an express written agreement signed by you and an authorized officer of the Company. Your last day of employment for any reason is referred to herein as the "Date of Termination." In the event that you elect to end your employment other than for Good Reason, the Company requires you to provide at least 30 days' advance written notice to the Company; and in the event that the Company terminates you without "Cause", you shall be given at least 30 days advance written notice by the Company. Notwithstanding the foregoing, the Company may unilaterally accelerate the Date of Termination, and such acceleration shall not result in a termination without Cause by the Company for purposes of this Agreement.

To the extent applicable, you shall be deemed to have resigned from all officer and board member positions that you hold with the Company or any of its respective subsidiaries and affiliates upon the termination of your employment for any reason. You shall execute any documents in reasonable form as may be requested to confirm or effectuate any such resignations.

9. Accrued Obligations. In the event of the ending of your employment for any reason, the Company shall pay you (i) your Base Salary and, if applicable, any accrued but unused vacation, through the Date of Termination, and (ii) the amount of any documented expenses properly incurred by you on behalf of the Company prior to any such termination and not yet reimbursed (the "Accrued Obligations").

10. Severance Pay and Benefits Outside of the Change in Control Period. As explained below, under certain circumstances you will be entitled to severance equal to the Severance Amount (as defined below), accelerated vesting of a portion of your unvested equity awards, plus continued employee benefits pursuant to COBRA (as defined below):

In the event that the Company terminates your employment without Cause or you terminate your employment with Good Reason, in either case, outside of the Change in Control Period (as such capitalized terms are defined in Appendix A), then, in addition to the Accrued Obligations, and subject to (i) your execution and non-revocation of a separation agreement and release in a form acceptable to the Company, which shall include a general release of claims against the Company and all related persons and entities and a reaffirmation of the Continuing Obligations (as defined below) and shall provide that if you breach the Continuing Obligations, all payments of the Severance Amount (as defined below) shall immediately cease (the "Separation Agreement and Release"), and (ii) the Separation Agreement and Release becoming irrevocable, all within 60 days after the Date of Termination (or such shorter period as set forth in the Separation Agreement and Release), which shall include a seven-day revocation period:

(a) The Company shall pay you an amount equal to 12 months of your Base Salary plus any bonus earned but unpaid for the year immediately prior to the year of termination (such salary and bonus together, the "Severance Amount").

(b) Notwithstanding anything to the contrary in any applicable equity-based award agreement or plan, the unvested portion of your then outstanding equity-based awards subject to time-based vesting (the "Time-Based Equity Awards") that would have vested within the 12-month period following the Termination Date shall immediately accelerate and become vested or nonforfeitable as of the later of (i) the Date of Termination or (ii) the effective date of the Separation Agreement and Release (such later date being the "Accelerated Vesting Date"); and provided further that any termination or forfeiture of the unvested portion of such Time-Based Equity Awards that would otherwise occur on the Date of Termination in the absence of this Agreement will be delayed until the effective date of the Separation Agreement and Release and will only occur if the vesting pursuant to this subsection does not occur due to the absence of the Separation Agreement and Release becoming fully effective within the time period set forth therein. Notwithstanding the foregoing, no additional vesting of the Time-Based Equity Awards shall occur during the period between the Date of Termination and the Accelerated Vesting Date.

(c) Subject to your copayment of premium amounts at the applicable active employees' rate and your proper election to receive benefits under the Consolidated Omnibus Budget Reconciliation Act of 1985, as amended ("COBRA"), the Company shall pay to the group health plan provider(s), the COBRA provider or you a monthly payment equal to the monthly employer contribution that the Company would have made to provide health insurance to you if you had remained employed by the Company until the earliest of (A) the 12-month anniversary of the Date of Termination; (B) your eligibility for group health plan benefits under any other employer's group health plan; or (C) the cessation of your continuation rights under COBRA; provided, however, that if the Company reasonably determines that it cannot pay such amounts to the group health plan provider(s) or the COBRA provider (if applicable) without potentially violating applicable law (including, without limitation, Section 2716 of the Public Health Service Act), then the Company shall convert such payments to payroll payments directly to you for the time period specified above. Such payments, if

to you, shall be subject to tax-related deductions and withholdings and paid on the Company's regular payroll dates.

The amounts payable under Section 10(a) and (c), to the extent taxable, shall be paid out in substantially equal installments in accordance with the Company's payroll practice over 12 months commencing within 60 days after the Date of Termination; provided, however, that if the 60-day period begins in one calendar year and ends in a second calendar year, the Severance Amount, to the extent it qualifies as "non-qualified deferred compensation" within the meaning of Section 409A of the Internal Revenue Code of 1986, as amended (the "Code"), shall begin to be paid in the second calendar year by the last day of such 60-day period; provided, further, that the initial payment shall include a catch-up payment to cover amounts retroactive to the day immediately following the Date of Termination. Each payment pursuant to this Agreement is intended to constitute a separate payment for purposes of Treasury Regulation Section 1.409A-2(b)(2).

Notwithstanding anything to the contrary in this Agreement, for the avoidance of doubt:

(i) if your employment ends for as a result of a termination by the Company for Cause or a resignation by you without Good Reason, you will be entitled to the Accrued Obligations and will not be entitled to any further compensation from the Company; and

(ii) if your employment ends due to your death or Disability, you will receive (i) the Accrued Obligations and (ii) all outstanding Time-Based Equity Awards shall immediately accelerate and become vested or nonforfeitable as of the Date of Termination, but will not be eligible for any other severance pay or benefits, whether pursuant to Section 10, Section 11 or otherwise.

11. Severance Pay and Benefits Within the Change in Control Period. In the event that the Company terminates your employment without Cause or you resign for Good Reason, in each case within the Change in Control Period, then, in addition to you being entitled to the Accrued Obligations, and subject to your execution and non-revocation of the Separation Agreement and Release and it becoming fully effective, all within 60 days after the Date of Termination (or such shorter period as set forth in the Separation Agreement and Release), which shall include a seven-day revocation period:

(a) The Company shall pay you an amount equal to (i) 18 months of your Base Salary plus (ii) any bonus earned but unpaid for the year immediately prior to the year of termination, plus (iii) your Target Bonus for the year in which the termination occurs (in each case, calculating by reference to your Base Salary rate as in effect immediately prior to your termination, but without giving effect to any prior reduction in Base Salary by the Company which would give rise to your right to resign for Good Reason) (such salary and bonuses together, the "CIC Severance Amount").

(b) Notwithstanding anything to the contrary in any applicable equity-based award agreement or plan, all of the unvested Time-Based Equity Awards shall immediately accelerate and become vested or nonforfeitable as of the Accelerated Vesting Date.

(c) All of your outstanding equity-based awards subject to performance-based vesting (the "Performance-Based Equity Awards") shall immediately accelerate and become vested or nonforfeitable as of the Accelerated Vesting Date with the performance criteria being deemed to have been met based on the greater of target or, if determinable, actual performance; provided,

however, that the applicable award agreement for any Performance-Based Equity Award may provide for alternative treatment upon a termination covered by this Section 11.

(d) The Company shall pay to the group health plan provider(s), the COBRA provider or you a monthly payment equal to the monthly COBRA continuation premiums until the earliest of (A) the 18-month anniversary of the Date of Termination; (B) your eligibility for group health plan benefits under any other employer's group health plan; or (C) the cessation of your continuation rights under COBRA; provided, however, that if the Company reasonably determines that it cannot pay such amounts to the group health plan provider(s) or the COBRA provider (if applicable) without potentially violating applicable law (including, without limitation, Section 2716 of the Public Health Service Act), then the Company shall convert such payments to payroll payments directly to you for the time period specified above. Such payments, if to you, shall be subject to tax-related deductions and withholdings and paid on the Company's regular payroll dates.

For the avoidance of doubt, Section 10 and Section 11 of this Agreement are mutually exclusive and in no event shall you be entitled to payments or benefits pursuant to both Section 10 and Section 11 of this Agreement.

12. Continuing Obligations.

(a) **EIACN Agreement**. As a condition of your employment, you are required to enter into an Employee Invention Assignment, Confidentiality and Non-Competition Agreement, which is enclosed with this Agreement (the "EIACN Agreement"), which must be signed prior to the Effective Date. For purposes of this Agreement, the obligations in this Section 12 and those that arise in the EIACN Agreement and any other agreement relating to confidentiality, assignment of inventions, or other restrictive covenants shall collectively be referred to as the "Continuing Obligations." You are advised to discuss the EIACN Agreement with an attorney of your choice, and you have had an adequate opportunity to do so prior to executing this Agreement or the EIACN Agreement.

(b) **Third Party Agreements and Rights**. You hereby confirm that you are not bound by the terms of any agreement with any previous employer or other party which would prevent you from performing your obligations hereunder. You represent to the Company that your execution of this Agreement, your employment with the Company and the performance of your proposed duties for the Company will not violate any obligations you may have to any such previous employer or other party. In your work for the Company, you will not disclose or make use of any information in violation of any agreements with or rights of any such previous employer or other party, and you will not bring to the premises of the Company any copies or other tangible embodiments of non-public information belonging to or obtained from any such previous employment or other party.

(c) **Litigation and Regulatory Cooperation**. You shall cooperate fully with the Company in (i) the defense or prosecution of any claims or actions now in existence or which may be brought in the future against or on behalf of the Company which relate to events or occurrences that transpired while you were engaged or employed by the Company, and (ii) the investigation, whether internal or external, of any matters about which the Company believes you may have knowledge or information. Your full cooperation in connection with such claims, actions or investigations shall include, but not be limited to, being reasonably available to meet with counsel to answer questions or to prepare for discovery or trial and to act as a witness on behalf of the Company at mutually convenient times. During and after your engagement and employment, you also shall cooperate fully with the Company in connection with any investigation or review of any federal, state or local

regulatory authority as any such investigation or review relates to events or occurrences that transpired while you were employed by the Company. The Company shall reimburse you for any reasonable out-of-pocket expenses incurred in connection with your performance of obligations pursuant to this Section 12(c).

(d) **Relief**. You agree that it would be difficult to measure any damages caused to the Company which might result from your breach of any of the Continuing Obligations, and that in any event money damages would be an inadequate remedy for any such breach. Accordingly, you agree that if you breach, or propose to breach, any portion of the Continuing Obligations, the Company shall be entitled, in addition to all other remedies that it may have, to seek an injunction or other appropriate equitable relief to restrain any such breach without showing or proving any actual damage to the Company.

13. Golden Parachute Taxes.

(a) **Best After-Tax Result**. In the event that any payment or benefit received or to be received by you pursuant to this Agreement or otherwise ("Payments") would (i) constitute a "parachute payment" within the meaning of Section 280G of the Code and (ii) but for this subsection (a), be subject to the excise tax imposed by Section 4999 of the Code, any successor provisions, or any comparable federal, state, local or foreign excise tax ("Excise Tax"), then, subject to the provisions of Section 14, such Payments shall be either (A) provided in full pursuant to the terms of this Agreement or any other applicable agreement, or (B) provided as to such lesser extent which would result in the Payments being $1.00 less than the amount at which any portion of the Payments would be subject to the Excise Tax, whichever of the foregoing amounts, taking into account the applicable federal, state, local and foreign income, employment and other taxes and the Excise Tax (including, without limitation, any interest or penalties on such taxes), results in the receipt, on an after-tax basis, of the greatest amount of payments and benefits provided for hereunder or otherwise, notwithstanding that all or some portion of such Payments may be subject to the Excise Tax. Unless the Company and you otherwise agree in writing, any determination required under this Section shall be made by independent tax counsel designated by the Company and reasonably acceptable to you ("Independent Tax Counsel"), whose determination shall be conclusive and binding upon you and the Company for all purposes. For purposes of making the calculations required under this Section, Independent Tax Counsel may make reasonable assumptions and approximations concerning applicable taxes and may rely on reasonable, good faith interpretations concerning the application of Sections 280G and 4999 of the Code; provided that Independent Tax Counsel shall assume that you pay all taxes at the highest marginal rate. The Company and you shall furnish to Independent Tax Counsel such information and documents as Independent Tax Counsel may reasonably request in order to make a determination under this Section. The Company shall bear all costs that Independent Tax Counsel may reasonably incur in connection with any calculations contemplated by this Section. In the event that Section 13(a)(ii)(B) above applies, then based on the information provided to you and the Company by Independent Tax Counsel, the cutback described hereunder will apply as to compensation not subject to Section 409A of the Code prior to compensation subject to Section 409A of the Code and will otherwise apply on a reverse chronological basis from payments latest in time. If the Internal Revenue Service (the "IRS") determines that any Payment is subject to the Excise Tax, then Section 13(b) hereof shall apply, and the enforcement of Section 13(b) shall be the exclusive remedy to the Company.

(b) **Adjustments**. If, notwithstanding any reduction described in Section 13(a) hereof (or in the absence of any such reduction), the IRS determines that you are liable for the Excise Tax as a result of the receipt of one or more Payments, then you shall be obligated to surrender or pay back to the Company within one-hundred 120 days after a final IRS determination, an amount of such payments or benefits equal to the "Repayment Amount." The Repayment Amount with respect to such Payments shall be the smallest such amount, if any, as shall be required to be surrendered or paid to the Company so that your net proceeds with respect to such Payments (after taking into account the payment of the Excise Tax imposed on such Payments) shall be maximized. Notwithstanding the foregoing, the Repayment Amount with respect to such Payments shall be zero if a Repayment Amount of more than zero would not eliminate the Excise Tax imposed on such Payments or if a Repayment Amount of more than zero would not maximize the net amount received from the Payments. If the Excise Tax is not eliminated pursuant to this Section 13(b), you shall pay the Excise Tax.

14. Section 409A.

(a) Anything in this Agreement to the contrary notwithstanding, if at the time of your separation from service within the meaning of Section 409A of the Code, the Company determines that you are a "specified employee" within the meaning of Section 409A(a)(2)(B)(i) of the Code, then to the extent any payment or benefit that you become entitled to under this Agreement or otherwise on account of your separation from service would be considered deferred compensation otherwise subject to the additional tax imposed pursuant to Section 409A(a) of the Code as a result of the application of Section 409A(a)(2)(B)(i) of the Code, such payment shall not be payable and such benefit shall not be provided until the date that is the earlier of (A) six months and one day after your separation from service, or (B) your death. If any such delayed cash payment is otherwise payable on an installment basis, the first payment shall include a catch-up payment covering amounts that would otherwise have been paid during the six-month period but for the application of this provision (without interest), and the balance of the installments shall be payable in accordance with their original schedule.

(b) All in-kind benefits provided and expenses eligible for reimbursement under this Agreement shall be provided by the Company or incurred by you during the time periods set forth in this Agreement. All reimbursements shall be paid as soon as administratively practicable, but in no event shall any reimbursement be paid after the last day of the taxable year following the taxable year in which the expense was incurred. The amount of in-kind benefits provided or reimbursable expenses incurred in one taxable year shall not affect the in-kind benefits to be provided or the expenses eligible for reimbursement in any other taxable year (except for any lifetime or other aggregate limitation applicable to medical expenses). Such right to reimbursement or in-kind benefits is not subject to liquidation or exchange for another benefit.

(c) To the extent that any payment or benefit described in this Agreement constitutes "non-qualified deferred compensation" under Section 409A of the Code, and to the extent that such payment or benefit is payable upon the termination of your employment, then such payments or benefits shall be payable only upon your "separation from service." The determination of whether and when a separation from service has occurred shall be made in accordance with the presumptions set forth in Treasury Regulation Section 1.409A-l(h).

(d) The parties intend that this Agreement will be administered in accordance with Section 409A of the Code. To the extent that any provision of this Agreement is ambiguous as to its compliance with Section 409A of the Code, the provision shall be read in such a manner so that all payments hereunder comply with Section 409A of the Code. Each payment pursuant to this Agreement is intended to constitute a separate payment for purposes of Treasury Regulation Section 1.409A-2(b)(2). The parties agree that this Agreement may be amended, as reasonably requested by either party, and as may be necessary to fully comply with Section 409A of the Code and all related rules and regulations in order to preserve the payments and benefits provided hereunder without additional cost to either party.

(e) The Company makes no representation or warranty and shall have no liability to you or any other person if any provisions of this Agreement are determined to constitute deferred compensation subject to Section 409A of the Code but do not satisfy an exemption from, or the conditions of, such Section.

15. Withholding; Tax Effect. All forms of compensation referred to in this Agreement are subject to reduction to reflect applicable withholding and payroll taxes and other deductions required by law. You hereby acknowledge that the Company does not have a duty to design its compensation policies in a manner that minimizes your tax liabilities, and you will not make any claim against the Company or the Board related to tax liabilities arising from your compensation.

16. Recoupment. Amounts paid or payable under this Agreement shall be subject to the provisions of any applicable clawback or recoupment policies or procedures adopted by the Company, which clawback or recoupment policies may provide for forfeiture and/or recoupment of amounts paid or payable under this Agreement. No forfeiture or recoupment under such policies or procedures will give rise to a right to resign for Good Reason or under any agreement between you and the Company.

17. Interpretation and Enforcement. This Agreement, together with Appendix A, the EIACN Agreement, any award agreement between you and the Company and the indemnification agreement between you and the Company, constitute the complete agreement between you and the Company, contains all of the terms of your employment with the Company. The terms of this Agreement and the resolution of any disputes as to the meaning, effect, performance or validity of this Agreement or arising out of, related to, or in any way connected with this Agreement, your employment with the Company or any other relationship between you and the Company (the "Disputes") will be governed by federal law to the extent applicable and otherwise by Massachusetts law, excluding laws relating to conflicts or choice of law and excluding Disputes arising in connection with any equity incentive plan, which shall be governed by the terms of the applicable equity incentive plan. You and the Company submit to the exclusive personal jurisdiction of the federal and state courts located in the Commonwealth of Massachusetts in connection with any Dispute or any claim related to any Dispute, except for Disputes arising under any equity incentive plan.

18. Assignment. Neither you nor the Company may make any assignment of this Agreement or any interest in it, by operation of law or otherwise, without the prior written consent of the other; provided, however, that the Company may assign its rights and obligations under this Agreement without your consent to any affiliate or to any person or entity with whom the Company shall hereafter effect a reorganization, consolidate with, or merge into or to whom it transfers all or substantially all of its properties or assets; provided further, that if you remain employed or become employed by the Company, the purchaser or any of their affiliates in connection with any such transaction, then you shall not be entitled to any payments, benefits or vesting pursuant to Section 10 or pursuant to Section 11 of this Agreement solely as a result of such transaction. This Agreement shall inure to the benefit of

and be binding upon you and the Company, and each of your and its respective successors, executors, administrators, heirs and permitted assigns.

19. Waiver; Amendment. No waiver of any provision hereof shall be effective unless made in writing and signed by the waiving party. The failure of any party to require the performance of any term or obligation of this Agreement, or the waiver by any party of any breach of this Agreement, shall not prevent any subsequent enforcement of such term or obligation or be deemed a waiver of any subsequent breach. This Agreement may be amended or modified only by a written instrument signed by you and by a duly authorized representative of the Company.

20. Enforceability. If any portion or provision of this Agreement (including, without limitation, any portion or provision of any section of this Agreement) shall to any extent be declared illegal or unenforceable by a court of competent jurisdiction, then the remainder of this Agreement, or the application of such portion or provision in circumstances other than those as to which it is so declared illegal or unenforceable, shall not be affected thereby, and each portion and provision of this Agreement shall be valid and enforceable to the fullest extent permitted by law.

21. Conditions. You must submit satisfactory proof of your identity, successfully complete a criminal background check, which you hereby expressly authorize by your execution of this Agreement, and provide documentation of your legal authorization to work in the United States on or prior to the Effective Date.

22. Employee Representations. It is the policy of the Company not to solicit or accept proprietary information and / or trade secrets of other companies or third parties. If you have or have had access to trade secrets or other confidential, proprietary information from your former employer or another third party, the use of such information in performing your duties at the Company is prohibited. This may include, but is not limited to, confidential or proprietary information in the form of documents, magnetic media, software, customer lists, and business plans or strategies.

In making this employment offer, the Company has relied on your representation that: (a) you are not currently a party to any agreement that would restrict your ability to accept this offer or to perform services for the Company; (b) you are not subject to any noncompetition or non-solicitation agreement or other restrictive covenants that might restrict your employment by the Company as contemplated by this offer; (c) you have the full right, power and authority to execute and deliver the Agreement and to perform all of your obligations thereunder; and (d) you will not bring with you to the Company or use in the performance of your responsibilities at the Company any materials, documents or work product of a former employer or other third party that are not generally available to the public, unless you have obtained written authorization from such former employer or third party for their possession and use and have provided the Company with a copy of same.

23. Other Terms. The provisions of this Agreement shall survive the termination of this Agreement and/or the termination of your employment to the extent necessary to effectuate the terms contained herein. The headings and other captions in this Agreement are for convenience and reference only and shall not be used in interpreting, construing or enforcing any of the provisions of this Agreement. This Agreement may be executed in separate counterparts. When both counterparts are signed, they shall be treated together as one and the same document. PDF copies of signed counterparts shall be equally effective as originals.

I look forward to working with you to make the Company a great success.

Sincerely,

/s/ Cameron Turtle
Name: Cameron Turtle
Title: Chief Operating Officer

Accepted and acknowledged:

/s/ Heidy King-Jones
Heidy King-Jones

Date: August 18, 2023

Appendix A

1. "Cause" shall mean (i) your dishonest statements or acts with respect to the Company or any affiliate of the Company, or any current or prospective customers, suppliers, vendors or other third parties with which such entity does business that results in or is reasonably anticipated to result in material harm to the Company; (ii) your conviction or plea of no contest to: (A) a felony or (B) any misdemeanor involving moral turpitude, deceit, dishonesty or fraud; (iii) your failure to perform in all material respects your lawful assigned duties and responsibilities to the reasonable satisfaction of the Board, which failure continues, in the reasonable judgment of the Board, for 30 days after written notice given to you describing such failure; (iv) your gross negligence, willful misconduct that results in or is reasonably anticipated to result in material harm to the Company; or (v) your violation of any material provision of any agreement(s) between you and the Company or any written Company policies including, without limitation, agreements relating to non-solicitation, non-disclosure and/or assignment of inventions or policies related to ethics or workplace conduct.

2. "Change in Control" shall have the meaning provided for the term "Corporate Transaction" under the Company's 2016 Equity Incentive Plan (or the meaning provided to any word of similar import under any successor plan).

3. "Change in Control Period" shall mean the period commencing three months prior to the first event constituting a Change in Control and ending 12 months following the first event constituting a Change in Control.

4. "Disability" shall mean a permanent and total disability as defined in Section 22(e) (3) of the Code.

5. "Good Reason" shall mean that you have complied with the Good Reason Process (hereinafter defined) following the occurrence, without your written consent, of any of the following events: (i) a material diminution in your base salary or Target Bonus except for across-the-board salary and target bonus reductions of no more than 10% based on the Company's financial performance similarly affecting all or substantially all senior management employees of the Company; (ii) a material change in the geographic location at which you are required to provide services to the Company or a requirement that you change your remote location from your then-current residence; (iii) a material reduction in your duties, authority or responsibilities; (iv) the failure of the Company to obtain the assumption of this Agreement by a successor; or (v) the material breach of this Agreement (or any other agreements with you) by the Company.

6. "Good Reason Process" shall mean that (i) you reasonably determine in good faith that a "Good Reason" condition has occurred; (ii) you notify the Company in writing of the first occurrence of the Good Reason condition within 60 days of the first occurrence of such condition; (iii) you cooperate in good faith with the Company's efforts, for a period not less than 30 days following such notice (the "Cure Period"), to remedy the condition; (iv) notwithstanding such efforts, the Good Reason condition continues to exist; and (v) you terminate your employment within 30 days after the end of the Cure Period. If the Company cures the Good Reason condition during the Cure Period, Good Reason shall be deemed not to have occurred.

Exhibit 10.20

CONSULTING AGREEMENT

THIS CONSULTING AGREEMENT (together with the attached Exhibit A (the "**Business Terms Exhibit**") and Exhibit B (the "**EU Data Privacy Exhibit**"), the "**Agreement**"), is made as of August 1, 2023 (the "**Effective Date**") by and between Aeglea BioTherapeutics, Inc., a Delaware corporation (the "**Company**"), and Mark McKenna ("**Consultant**"). The Company desires to have the benefit of Consultant's knowledge and experience, and Consultant desires to provide services to the Company, all as provided in this Agreement.

1. **Services.** The Company retains Consultant, and Consultant agrees to provide, consulting and advisory services to the Company as the Company from time to time may reasonably request and as specified in the Business Terms Exhibit (the "**Consulting Services**"). Any changes to the Consulting Services (and any related compensation adjustments) must be agreed to in writing between Consultant and the Company prior to implementation of the changes.

2. **Compensation.** As full consideration for Consulting Services provided under this Agreement, the Company agrees to pay Consultant and reimburse expenses as described in the Business Terms Exhibit.

3. **Performance.** Consultant agrees to provide the Consulting Services to the Company, or to its designee, in accordance with all applicable laws and regulations and the highest professional standards. Consultant represents and warrants that Consultant has not been, and is not under consideration to be (a) debarred from providing services pursuant to Section 306 of the United States Federal Food Drug and Cosmetic Act, 21 U.S.C. § 335a; (b) excluded, debarred or suspended from, or otherwise ineligible to participate in, any federal or state health care program or federal procurement or non-procurement programs (as that term is defined in 42 U.S.C. § 1320a-7b(f)); (c) disqualified by any government or regulatory agencies from performing specific services, and is not subject to a pending disqualification proceeding; or (d) convicted of a criminal offense related to the provision of health care items or services, or under investigation or subject to any such action that is pending.

4. **Compliance with Obligations to Third Parties.** Consultant represents and warrants to the Company that the terms of this Agreement and Consultant's performance of Consulting Services do not and will not conflict with any of Consultant's obligations to any third parties. Consultant agrees not to use any trade secrets or other confidential information of any other person, firm, corporation, institution or other third party in connection with any of the Consulting Services. If Consultant is an employee of another company or institution, Consultant represents and warrants that Consultant is permitted to enter into this Agreement pursuant to such company's or institution's policies concerning professional consulting and additional workload. Consultant agrees not to make any use of any funds, space, personnel, facilities, equipment or other resources of a third party in performing the Consulting Services, nor take any other action that would result in a third party asserting ownership of, or other rights in, any Work Product (defined in Section 5), unless agreed upon in writing in advance by the Company.

5. **Work Product.** Consultant will promptly and fully disclose in confidence to the Company all inventions, discoveries, improvements, ideas, concepts, designs, processes, formulations, products, computer programs, works of authorship, databases, mask works,

trade secrets, know-how, information, data, documentation, reports, research, creations and other products arising from or made in the performance of (solely or jointly with others) the Consulting Services (whether or not patentable or subject to copyright or trade secret protection) (collectively, the "**Work Product**"). Consultant assigns and agrees to assign to the Company all rights in the United States and throughout the world to Work Product. Consultant will keep and maintain adequate and current written records of all Work Product, and such records will be available to and remain the sole property of the Company at all times. For purposes of the copyright laws of the United States, Work Product will constitute "works made for hire," except to the extent such Work Product cannot by law be "works made for hire". Consultant represents and warrants that Consultant has and will have the right to transfer and assign to the Company ownership of all Work Product. Consultant will execute all documents, and take any and all actions needed, all without further consideration, in order to confirm the Company's rights as outlined above. In the event that Consultant should fail or refuse to execute such documents within a reasonable time, Consultant appoints the Company as attorney to execute and deliver any such documents on Consultant's behalf.

6. Confidentiality.

6.1 Definition. "**Confidential Information**" means (a) any non-public scientific, technical, business or financial information or trade secrets in whatever form (written, oral or visual) that is furnished or made available to Consultant by or on behalf of the Company; (b) all information contained in or comprised of Company Materials (defined in Section 7); and (c) all Work Product. Confidential Information is, and will remain, the sole property of the Company.

6.2 Obligations. During the Term (as defined in Section 9) and thereafter, Consultant agrees to (a) hold in confidence all Confidential Information, and not disclose Confidential Information without the prior written consent of the Company; (b) use Confidential Information solely in connection with the Consulting Services; (c) treat Confidential Information with no less than a reasonable degree of care; (d) reproduce Confidential Information solely to the extent necessary to provide the Consulting Services, with all such reproductions being considered Confidential Information; and (e) notify the Company of any unauthorized disclosure of Confidential Information promptly upon becoming aware of such disclosure. If Consultant is required by a governmental authority or by order of a court of competent jurisdiction to disclose any Confidential Information, Consultant will give the Company prompt written notice thereof and Consultant will take all reasonable and lawful actions to avoid or minimize the degree of such disclosure. Consultant will cooperate reasonably with the Company in any efforts to seek a protective order.

6.3 Exceptions. Consultant's obligations of non-disclosure and non-use under this Agreement will not apply to any portion of Confidential Information that Consultant can demonstrate, by competent proof:

(a) is generally known to the public at the time of disclosure or becomes generally known through no wrongful act on the part of Consultant;

(b) is in Consultant's possession at the time of disclosure other than as a result of Consultant's breach of any legal obligation;

(c) becomes known to Consultant on a non-confidential basis through disclosure by sources other than the Company having the legal right to disclose such Confidential Information; or

(d) is independently developed by Consultant without reference to or reliance upon Confidential Information.

6.4 Defend Trade Secrets Act. The Company provides notice to Consultant that pursuant to the United States Defend Trade Secrets Act of 2016:

(a) An individual will not be held criminally or civilly liable under any United States federal or state trade secret law for the disclosure of a trade secret that is made (i) in confidence to a federal, state, or local government official or to an attorney, and solely for the purpose of reporting or investigating a suspected violation of law; or (ii) in a complaint or other document filed in a lawsuit or other proceeding, if such filing is made under seal; and

(b) An individual who files a lawsuit for retaliation by an employer for reporting a suspected violation of law may disclose the trade secret to the attorney of the individual and use the trade secret information in the court proceeding, if the individual (i) files any document containing the trade secret under seal; and (ii) does not disclose the trade secret, except pursuant to court order.

In addition, this Agreement does not prohibit Consultant from participating in or cooperating with any government investigation or proceeding, nor does this Agreement restrict Consultant from disclosing Confidential Information to government agencies in a reasonable manner when permitted by applicable state or federal "whistleblower" or other laws.

6.5 Personal Identifiable Information.

(a) In General. Notwithstanding anything to the contrary in this Section 6, to the extent that Consultant may, during or as a result of rendering Consulting Services, have access to any information that could be used to identify an individual ("**Personal Identifiable Information**"), (i) Consultant will not disclose to any third party nor use such Personal Identifiable Information other than to provide the Consulting Services and as long as such disclosure and use is in compliance with applicable law; and (ii) such restrictions on the disclosure and use of Personal Identifiable Information will remain in place for as long as such restrictions are required under applicable law.

(b) EU Data Protection. Without limiting the generality of Section 6.5(a), to the extent Consultant may, during or as a result of rendering Consulting Services, have access to European Union-originating Personal Data, as that term is defined in the General Data Protection Regulation (EU) 2016/679 (the "**GDPR**"), the terms set forth in the EU Data Privacy Exhibit will apply in addition to the other terms and conditions of this Agreement.

7. Company Materials. All documents, data, records, materials, compounds, apparatus, equipment and other physical property furnished or made available by or on behalf of the

Company to Consultant in connection with this Agreement ("**Company Materials**") are and will remain the sole property of the Company. Consultant will use Company Materials only as necessary to perform the Consulting Services and will not transfer or make available to any third party the Company Materials without the express prior written consent of the Company. Consultant will return to the Company any and all Company Materials upon request.

8. **Publication; Publicity.** Consultant may not publish or refer to Work Product, in whole or in part, without the prior express written consent of the Company. Consultant will not use the name, logo, trade name, service mark, or trademark, or any simulation, abbreviation, or adaptation of same, or the name of the Company or any of its affiliates for publicity, promotion, or other uses without the Company's prior written consent.

9. **Expiration/Termination.** The term of this Agreement will commence on the Effective Date and expire at the end of the period specified in the "Term" Section of the Business Terms Exhibit, unless sooner terminated pursuant to the provisions of this Section 9 or extended by mutual written agreement of the parties (the "**Term**"). The Company may terminate this Agreement at any time with or without cause upon not less than ten (10) days' prior written notice to Consultant. Consultant may terminate this Agreement at any time with or without cause upon not less than sixty (60) days' prior written notice to the Company. Any expiration or termination of this Agreement shall be without prejudice to any obligation of either party that has accrued prior to the effective date of expiration or termination. Upon expiration or termination of this Agreement, neither Consultant nor the Company will have any further obligations under this Agreement, except that (a) Consultant will terminate all Consulting Services in progress in an orderly manner as soon as practicable and in accordance with a schedule agreed to by the Company, unless the Company specifies in the notice of termination that Consulting Services in progress should be completed; (b) Consultant will deliver to the Company all Work Product made through expiration or termination; (c) the Company will pay Consultant any monies due and owing Consultant, up to the time of termination or expiration, for Consulting Services properly performed and all authorized expenses actually incurred; (d) Consultant will immediately return to the Company all Company Materials and other Confidential Information and copies thereof provided to Consultant under this Agreement; and (e) the terms, conditions and obligations under Sections 3 (last sentence), 4, 5, 6, 7, 8, 9, and 10 and the EU Data Privacy Exhibit will survive expiration or termination of this Agreement.

10. **Miscellaneous.**

10.1 Independent Contractor. The parties understand and agree that Consultant is an independent contractor and not an agent or employee of the Company. Consultant has no authority to obligate the Company by contract or otherwise. Consultant will not be eligible for any employee benefits of the Company and expressly waives any rights to any employee benefits. Except as otherwise required by law, Consultant will bear sole responsibility for paying and reporting Consultant's own applicable federal and state income taxes, social security taxes, unemployment insurance, workers' compensation, and health or disability insurance, retirement benefits, and other welfare or pension benefits, if any, and indemnifies and holds the Company harmless from and against any liability with respect to such taxes, benefits and other matters.

10.2 Use of Name. Consultant consents to the use by the Company of Consultant's name on its website, in press releases, company brochures, offering documents, presentations, reports or other documents in printed or electronic form, and any documents filed with or submitted to any governmental or regulatory agency or any

securities exchange or listing entity; *provided*, that such materials or presentations accurately describe the nature of Consultant's relationship with or contribution to the Company.

10.3 Entire Agreement. This Agreement contains the entire agreement of the parties with regard to its subject matter, and supersedes all prior or contemporaneous written or oral representations, agreements and understandings between the parties relating to that subject matter. This Agreement may be changed only by a writing signed by Consultant and an authorized representative of the Company.

10.4 Assignment and Binding Effect. The Consulting Services to be provided by Consultant are personal in nature. Consultant may not assign or transfer this Agreement or assign, transfer or subcontract any of Consultant's rights or obligations under this Agreement. The Company may transfer or assign this Agreement, in whole or in part, without the prior written consent of Consultant. Any purported assignment or transfer in violation of this Section is void. This Agreement will be binding upon and inure to the benefit of the parties and their respective legal representatives, heirs, successors and permitted assigns.

10.5 Notices. All notices required or permitted under this Agreement must be in writing and must be given by directing the notice to the address for the receiving party set forth in this Agreement or at such other address as the receiving party may specify in writing under this procedure. Notices to the Company will be marked "Attention: Board of Directors". All notices must be given (a) by personal delivery, with receipt acknowledged; (b) by prepaid certified or registered mail, return receipt requested; or (c) by prepaid recognized next business day delivery service. Notices will be effective upon receipt or at a later date stated in the notice.

10.6 Governing Law. This Agreement and any disputes relating to or arising out of this Agreement will be governed by, construed, and interpreted in accordance with the internal laws of the State of Delaware, without regard to any choice of law principle that would require the application of the law of another jurisdiction. The parties agree to submit to the exclusive jurisdiction of the state and federal courts located in the State of Delaware and waive any defense of inconvenient forum to the maintenance of any action or proceeding in such courts.

10.7 Severability; Reformation. Each provision in this Agreement is independent and severable from the others, and no provision will be rendered unenforceable because any other provision is found by a proper authority to be invalid or unenforceable in whole or in part. If any provision of this Agreement is found by such an authority to be invalid or unenforceable in whole or in part, such provision shall be changed and interpreted so as to best accomplish the objectives of such unenforceable or invalid provision and the intent of the parties, within the limits of applicable law.

10.8 No Strict Construction; Headings. This Agreement has been prepared jointly and will not be strictly construed against either party. The Section headings are included solely for convenience of reference and will not control or affect the meaning or interpretation of any of the provisions of this Agreement.

10.9 Waivers. Any delay in enforcing a party's rights under this Agreement, or any waiver as to a particular default or other matter, will not constitute a waiver of such party's rights to the future enforcement of its rights under this Agreement, except with respect to an express written waiver relating to a particular matter for a particular period

of time signed by Consultant and an authorized representative of the waiving party, as applicable.

10.10 Remedies. Consultant agrees that (a) the Company may be irreparably injured by a breach of this Agreement by Consultant; (b) money damages would not be an adequate remedy for any such breach; (c) as a remedy for any such breach the Company will be entitled to seek equitable relief, including injunctive relief and specific performance, without being required by Consultant to post a bond; and (d) such remedy will not be the exclusive remedy for any breach of this Agreement.

10.11 Counterparts. This Agreement may be executed in any number of counterparts, each of which will be deemed an original, but all of which together will constitute one and the same instrument. A facsimile or portable document format (".pdf") copy of this Agreement, including the signature pages, will be deemed an original.

[Signature page follows]

IN WITNESS WHEREOF, the parties have executed this Agreement as of the Effective Date.

AEGLEA BIOTHERAPEUTICS, INC.	**Mark McKenna**
By: /s/ Cameron Turtle	/s/ Mark McKenna
Name: Cameron Turtle	
Title: Chief Executive Officer	

EXHIBIT A

BUSINESS TERMS EXHIBIT

1. Consulting Services:

Consultant will provide the following Consulting Services to the Company:

Senior advisor to the executive management team, providing guidance related to organizational and corporate development as well as scientific and clinical strategy.

Consultant will provide Consulting Services on a schedule and at a location or locations as mutually agreed between Consultant and the Chief Executive Officer or the Chief Operating Officer of the Company. In addition, Consultant will be available for a reasonable number of telephone and/or written consultations.

2. Compensation:

Stock Options: Subject to approval by the Company's Board of Directors (the "**Board**"), the Company will grant Consultant nonqualified stock options to purchase 477,000 shares of the Company's common stock ("**Common Stock**"), with an exercise price determined by the Board on the date of grant (the "**Options**"). The Options will vest in accordance with the following vesting schedule: (a) prior to the first one (1) year anniversary of the Effective Date (the "**Vesting Commencement Date**"), the Options will not be vested or exercisable as to any of the underlying shares; (b) the Options will become vested and exercisable with respect to 1/4th of the underlying shares on the one (1) year anniversary of the Vesting Commencement Date; and (c) thereafter, the Options will become vested and exercisable with respect to an additional 1/48th of the underlying shares when Consultant completes each month of continuous service following the first one (1) year anniversary of the Vesting Commencement Date. The Options will be governed by the terms of the related award agreement, the Company's 2016 Equity Incentive Plan and the terms and conditions approved by the Board. Notwithstanding the foregoing, if Consultant does not commence services for the Company within two months following the Effective Date, the Company may, in its sole discretion, cancel the Options for no consideration.

Expenses: The Company will reimburse Consultant for any pre-approved expenses actually incurred by Consultant in connection with the provision of Consulting Services. Requests for reimbursement will be in a form reasonably acceptable to the Company and will include supporting documentation.

3. Term:

This Agreement will be for a term of four (4) years beginning on the Effective Date.

EXHIBIT B

EU DATA PRIVACY EXHIBIT

DATA PROCESSING TERMS

For purposes of this EU Data Privacy Exhibit, capitalized terms used but not defined in this Exhibit will have the meaning ascribed to them in the GDPR. The Company will serve as the Controller and Consultant will serve as the Company's Processor in respect of all Personal Data made available to Consultant in connection with the provision of the Consulting Services under this Agreement. As a Processor of any such Personal Data, Consultant will:

(a) Process Personal Data solely for the purposes of providing the Consulting Services and in accordance with the Company's written instructions and not for any other purpose or in any other manner;

(b) not disclose or transfer Personal Data to any third party without the Company's prior written consent, except as permitted under this Agreement;

(c) use diligent efforts to promptly (i) investigate and remediate any Personal Data Breach by Consultant to prevent a recurrence of such breach; (ii) respond to any request for information from or complaint by a data protection authority/Supervisory Authority in relation to Personal Data that Consultant Processes for the purpose of providing the Consulting Services; and (iii) respond to any request made to Consultant by a Data Subject to exercise rights such as to access, rectify, amend, correct, share, delete or cease Processing his or her Personal Data;

(d) retain Personal Data for the longer of the time period necessary to perform the Processing Services or as required by applicable law;

(e) allow the Company or its designee to audit compliance with this EU Data Privacy Exhibit with advance notice and during normal business hours; and

(f) ensure that transfers of Personal Data outside of the European Economic Area are made only in accordance with EU or Member State law and pursuant to a framework deemed adequate and approved by the European Commission.

Exhibit 21.1

Subsidiaries of Spyre Therapeutics, Inc.

Name of Subsidiary	Jurisdiction
Spyre Therapeutics LLC	Delaware
Aeglea Development Company, Inc.	Delaware
AERase, Inc.	Delaware
AECase, Inc.	Delaware
AEMase, Inc.	Delaware
AE4ase, Inc.	Delaware
AE5ase, Inc.	Delaware
AE6ase, Inc.	Delaware
Aeglea Biotherapeutics UK Limited	England and Wales
Aeglea Ireland Limited	Ireland
Aeglea BioTherapeutics US LLC	Delaware

DOCPROPERTY "DOCID" * MERGEFORMAT

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-8 (Nos. 333-210633, 333-216903, 333-223614, 333-230137, 333-236584, 333-254430, 333-263357, 333-270208 and 333-276256) of Spyre Therapeutics, Inc. of our report dated February 29, 2024 relating to the financial statements, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP

Austin, Texas
February 29, 2024

Exhibit 31.1

Certification of Periodic Report under Section 302 of the Sarbanes-Oxley Act of 2002

I, Cameron Turtle, certify that:

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

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

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

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

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

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

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

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

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

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

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

Date: February 29, 2024

/s/ Cameron Turtle, D.Phil

Cameron Turtle, D.Phil

Chief Executive Officer

(Principal Executive Officer)

Exhibit 31.2

Certification of Periodic Report under Section 302 of the Sarbanes-Oxley Act of 2002

I, Scott Burrows, certify that:

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

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

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

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

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

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

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

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

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

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

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

Date: February 29, 2024

/s/ Scott Burrows

Scott Burrows

Chief Financial Officer

(Principal Financial Officer and Principal Accounting Officer)

Exhibit 32.1

Certification
Pursuant To 18 U.S.C. Section 1350,
As Adopted Pursuant To
Section 906 of The Sarbanes-Oxley Act Of 2002

In connection with the Annual Report of Spyre Therapeutics, Inc. (the "Company") on Form 10-K for the year ended December 31, 2023, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), each of the undersigned officers of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to the best of his knowledge:

1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

2) The information contained in the Report fairly presents, in all material respects, the financial condition of the Company and results of operations of the Company.

Date: February 29, 2024

/s/ Cameron Turtle, D.Phil

Cameron Turtle, D.Phil
Chief Executive Officer
(Principal Executive Officer)

/s/ Scott Burrows

Scott Burrows
Chief Financial Officer
(Principal Financial Officer and Principal Accounting Officer)

Exhibit 97

SPYRE THERAPEUTICS, INC.
COMPENSATION RECOUPMENT (CLAWBACK) POLICY

(Adopted By Board on October 25, 2023)

Recoupment of Incentive-Based Compensation

It is the policy of Spyre Therapeutics, Inc. (the "Company") that, in the event the Company is required to prepare an accounting restatement of the Company's financial statements due to the Company's material non-compliance with any financial reporting requirement under the federal securities laws (including any such correction that is material to the previously issued financial statements, or that would result in a material misstatement if the error were corrected in the current period or left uncorrected in the current period), the Company will recover on a reasonably prompt basis the amount of any Incentive-Based Compensation Received by a Covered Executive during the Recovery Period that exceeds the amount that otherwise would have been Received had it been determined based on the restated financial statements.

Policy Administration and Definitions

This Compensation Recoupment (Clawback) Policy (this "Policy") is administered by the Compensation Committee (the "Committee") of the Company's Board of Directors and is intended to comply with, and as applicable to be administered and interpreted consistent with, and subject to the exceptions set forth in, Listing Standard 5608 adopted by The Nasdaq Stock Market to implement Rule 10D-1 under the Securities Exchange Act of 1934, as amended (collectively, "Rule 10D-1").

For purposes of this Policy:

"Incentive-Based Compensation" means any compensation granted, earned, or vested based in whole or in part on the Company's attainment of a financial reporting measure that was Received by a person (i) on or after October 2, 2023 and after the person began service as a Covered Executive, and (ii) who served as a Covered Executive at any time during the performance period for the Incentive-Based Compensation. A financial reporting measure is (A) any measure that is determined and presented in accordance with the accounting principles used in preparing the Company's financial statements and any measure derived wholly or in part from such a measure, and (B) any measure based in whole or in part on the Company's stock price or total shareholder return.

Incentive-Based Compensation is deemed to be "Received" in the fiscal period during which the relevant financial reporting measure is attained, regardless of when the compensation is actually paid or awarded.

"Covered Executive" means any "executive officer" of the Company as defined under Rule 10D-1.

"Recovery Period" means the three completed fiscal years immediately preceding the date that the Company is required to prepare the accounting restatement described in this Policy, all as determined pursuant to Rule 10D-1, and any transition period of less than nine months that is within or immediately following such three fiscal years.

If the Committee determines the amount of Incentive-Based Compensation Received by a Covered Executive during a Recovery Period exceeds the amount that would have been Received if determined or calculated based on the Company's restated financial results, such excess amount of Incentive-Based Compensation shall be subject to recoupment by the Company pursuant to this Policy. For Incentive-Based Compensation based on stock price or total shareholder return, where the amount of erroneously awarded compensation is not subject to mathematical recalculation directly from the information in an accounting restatement, the Committee will determine the amount based on a reasonable estimate of the effect of the accounting restatement on the relevant stock price or total shareholder return. In all cases, the calculation of the excess amount of Incentive-Based Compensation to be recovered will be determined without regard to any taxes paid with respect to such compensation. The Company will maintain and will provide to the Nasdaq Stock Market documentation of all determinations and actions taken in complying with this Policy. Any determinations made by the Committee under this Policy shall be final and binding on all affected individuals.

The Company may effect any recovery pursuant to this Policy by requiring payment of such amount(s) to the Company, by set-off, by reducing future compensation, or by such other means or combination of means as the Committee determines to be appropriate. The Company need not recover the excess amount of Incentive-Based Compensation if and to the extent that the Committee determines that such recovery is impracticable, subject to and in accordance with any applicable exceptions under the Nasdaq Stock Market listing rules, and not required under Rule 10D-1, including if the Committee determines that the direct expense paid to a third party to assist in enforcing this Policy would exceed the amount to be recovered after making a reasonable attempt to recover such amounts. The Company is authorized to take appropriate steps to implement this Policy with respect to Incentive-Based Compensation arrangements with Covered Executives.

Any right of recoupment or recovery pursuant to this Policy is in addition to, and not in lieu of, any other remedies or rights of recoupment that may be available to the Company pursuant to the terms of any other policy, any employment agreement or plan or award terms, and any other legal remedies available to the Company; provided that the Company shall not recoup amounts pursuant to such other policy, terms or remedies to the extent it is recovered pursuant to this Policy. The Company shall not indemnify any Covered Executive against the loss of any Incentive-Based Compensation (or provide any advancement of expenses in such instance), including any payment or reimbursement for the cost of third-party insurance purchased by any Covered Executives to fund potential recovery obligations under this Policy.