REFINITIV

DELTA REPORT

10-K

TRVI - TREVI THERAPEUTICS, INC.

10-K - DECEMBER 31, 2023 COMPARED TO 10-K - DECEMBER 31, 2022

The following comparison report has been automatically generated

TOTAL DELTAS	3537
CHANGES	235
DELETIONS	1721
ADDITIONS	1581

REFINITIV

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2022 2023

OR

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

Commission File Number 001-38886

TREVI THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**45-0834299**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
195 Church Street, 16th Floor New Haven, Connecticut	**06510**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (203) 304-2499

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

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.001 par value per share	**TRVI**	**The Nasdaq Stock Market LLC**

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

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

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

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

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, 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 officers during the relevant recovery period pursuant to §240.10D-1(b). ☐

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

As of June 30, 2022 June 30, 2023, the last business day of the Registrant's most recently completed second fiscal quarter, the aggregate market value of the voting and non-voting common equity held by non-affiliates of the Registrant, based on the closing price of the shares of common stock on The Nasdaq Stock Market, was $65.2 105.6 million.

The number of shares of Registrant's Common Stock outstanding as of March 16, 2023 March 20, 2024 was 60,045,096 68,960,167.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Proxy Statement for the registrant's 2023 2024 Annual Meeting of Stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS AND INDUSTRY DATA

This Annual Report on Form 10-K contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical fact, contained in this Annual Report on Form 10-K, including statements regarding our strategy, future operations, future financial position, future revenues and profitability, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "might," "plan," "potential," "predict," "project," "should," "target," "would," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this Annual Report on Form 10-K include, among other things, statements about:

- our clinical trials, including our planned trials Phase 2b CORAL clinical trial of Haduvio for the treatment of chronic cough in adults with idiopathic pulmonary fibrosis, or IPF, and for refractory chronic cough and our Phase 2b/3 PRISM 2a RIVER clinical trial of Haduvio for the treatment of prurigo nodularis; refractory chronic cough, or RCC, ar our Phase 1b clinical trial to evaluate the effect of Haduvio on respiratory physiology in patients with IPF of varying disease severity as well as our human abuse potential, or HAP, study to compare the abuse potential of oral nalbuphine to intravenous, or IV, butorphanol;
- our plans to develop and, if approved, subsequently commercialize Haduvio for the treatment of chronic cough in adults with IPF and for other chronic cough indications RCC and for the treatment of prurigo nodularis;

- our expectations regarding the timing for the initiation of clinical trials and the reporting of data from such trials;
- the timing of and our ability to submit applications for and to obtain and maintain regulatory approvals for Haduvio;
- our expectations regarding our ability to fund our operating expenses, including our ongoing and planned clinical trials, and our capital expenditure requirements with our cash, cash equivalents and marketable securities;
- our estimates regarding expenses, future revenue, timing of any future revenue, capital requirements and needs for additional financing;
- the impact of government laws and regulations;
- our competitive position; and
- our ability to establish and maintain collaborations; and
- the impact of the COVID-19 pandemic and other outbreaks of infectious disease on our clinical trials, business and operations, and our response to the COVID-19 pandemic and any other such outbreaks. collaborations.

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

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

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

We own or have rights to trademarks, service marks and trade names that we use in connection with the operation of our business, including our corporate name, logos and website names. We own the trademarks Trevi® and Haduvio™. Other trademarks, service marks and trade names appearing in this Annual Report on Form 10-K are the property of their respective owners. Solely for convenience, some of the trademarks, service marks and trade names referred to in this

Annual Report on Form 10-K are listed without the ® and ™ symbols, but we will assert, to the fullest extent under applicable law, our rights to our trademarks, service marks and trade names. We intend to propose Haduvio as the trade name for our oral nalbuphine ER investigational product.

RISK FACTOR SUMMARY

The following is a summary of the principal factors that make an investment in our company speculative or risky. This summary does not address all of the risks and uncertainties that we face. Additional risk and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. Additional discussion of the risks summarized in this summary and other risks that we face, can be found in the “Risk Factors” section of this Annual Report on Form 10-K, and should be carefully considered, together with other information in this Annual Report on Form 10-K and our other filings with the Securities and Exchange Commission, before making an investment decision regarding our common stock. The forward-looking statements discussed above are qualified by these risk factors. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected.

- We have incurred significant losses since inception and expect to continue to incur significant and increasing losses f the foreseeable future. We may never achieve or maintain profitability.

- We will need substantial additional funding. If we are unable to raise sufficient capital when needed on acceptable terms or at all, we could be forced to delay, reduce or abandon our product development programs or commercialization efforts.

- We are dependent on the successful development and commercialization of Haduvio, our sole product candidate. If v are unable to complete the clinical development of, obtain marketing approval for or successfully commercialize Haduvio or if we experience significant delays in doing so, our business would be substantially harmed.

- We are in the process of designing future clinical trials of Haduvio for the treatment of chronic cough in adults with IPF and refractory chronic cough. Before commencing the trials, we plan to discuss the design of the trials with regulatory authorities and will need to submit do not yet have an open investigational new drug application, or IND, for Haduvio before proceeding with our planned trials for chronic cough in adults IPF. We expect to have an active IND for our planned Phase 1b clinical trial to evaluate the effect of Haduvio on respiratory physiology in patients with IPF at sites varying disease severity in the United States. Changes in the design first half of planned trials or regulatory 2024. Regulatory delays may affect the timing and costs of the this trial as well as other trials and changes in the timing or costs of the trials for these or other reasons chronic cough in IPF and may affect our ability to complete the planned o ongoing trials with our existing cash resources.

- The outcome of clinical trials may not be predictive of the success of later clinical trials. For instance, Haduvio may fa to show the desired safety and efficacy in clinical development despite demonstrating positive results in earlier clinica trials. The results of our Phase 2 clinical trial of Haduvio for the treatment of chronic cough in IPF, which we refer to a the Phase 2 CANAL trial, may not be predictive of the results of future trials of Haduvio for the treatment of chronic cough in adults with IPF or other chronic cough indications such as refractory chronic cough, RCC, and the results of our Phase 2b/3 clinical trial of Haduvio in patients with prurigo nodularis, which we refer to as our Phase 2b/3 PRISM trial, in Haduvio for the treatment of prurigo nodularis may not be predictive of the results of any future trial in prurigo nodularis.

- We have experienced delays and difficulties in the enrollment of subjects patients in our clinical trials in the past, including in our Phase 2 CANAL trial and our Phase 2b/3 PRISM trial. If we experience delays or difficulties in the enrollment of subjects patients in current or future clinical trials, our receipt of necessary regulatory approvals could b delayed or prevented. Other companies are conducting clinical trials or have announced plans for future clinical trials that are seeking or are likely to seek to enroll subjects patients with chronic cough with IPF, refractory chronic cough RCC and prurigo nodularis, and subjects patients are generally only able to enroll in a single trial at a time. In addition, many patients use various treatments off-label to treat chronic cough associated with IPF, refractory chronic cough RCC and prurigo nodularis, and these patients and their physicians may be reluctant to forgo, discontinue or otherwise alter their use of such off-label therapeutic approaches to participate in our clinical trials.

- Clinical drug development involves a lengthy and expensive process with an uncertain outcome. Even if we complete the necessary preclinical studies and clinical trials, the regulatory approval process is expensive, time-consuming and uncertain, which may prevent us from obtaining approvals for the commercialization of Haduvio or any future product candidate.

- Adverse events or undesirable side effects caused by, or other unexpected properties of, Haduvio or any future proje candidate may be identified during development and could delay or prevent the marketing approval or limit the use of Haduvio or any future product. Haduvio, as a mixed κ-opioid receptor agonist and μ-opioid receptor antagonist, may b susceptible to side effects associated with drugs having either of those mechanisms of action, including psychiatric si effects, withdrawal effects, respiratory depression and potential cardiac risk, as well as endocrine side effects associated with opioids generally.

- The drug label for nalbuphine, the active ingredient in Haduvio, carries an opioid class label warning for serious, life-threatening or fatal respiratory depression and Haduvio, if approved for marketing in any indication, will

---

likely carry a similar opioid class label. We intend to conduct a Phase 1b study of Haduvio to assess evaluate the risk effect of Haduvio on respiratory depression physiology in patients with IPF. IPF of varying disease severity. We cannot be certain that respiratory depression will not be observed or that the U.S. Food and Drug Administration, or FDA, will not require additional trials or impose more severe labeling restrictions related to respiratory depression. If there is a safety signal in the Phase 1b study, it could affect our ability to conduct a trial in this patient population.

- Many currently approved μ-opioid products are subject to restrictive marketing and distribution regulations which, if applied to Haduvio, could potentially restrict its use and harm our ability to generate profits. We are conducting a human abuse liability, or HAL, HAP study to determine compare the abuse potential of oral nalbuphine ER relative to butorphanol. If the results of the HAL HAP study suggest that Haduvio may carry risks of misuse, abuse or addiction even if the trial indicates that Haduvio does not carry such risks, the U.S. Food and Drug Administration, or FDA may require us to implement a Risk Evaluation and Mitigation Strategy in connection with any commercialization of Haduv and the U.S. Drug Enforcement Agency could determine that Haduvio should be classified as a controlled substance.

- If we are unable to establish sales, marketing and distribution capabilities or enter into sales, marketing and distributi arrangements with third parties, we may not be successful in commercializing Haduvio or any future product candidat if and when they are approved.

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

- We contract with third parties to conduct our clinical trials and for the manufacture, storage, packaging and distributio of Haduvio for clinical trials, including a single supplier for the active ingredient in Haduvio. We expect to continue to rely on third parties for these services in connection with our future development and commercialization efforts for Haduvio. If they do not perform satisfactorily, our business could be harmed.

- If we fail to comply with our obligations under our existing and any future intellectual property licenses with third partie including our license with Endo Pharmaceuticals Inc., we could lose license rights that are critical to our business or owe damages to the licensor of such intellectual property.

- If we are unable to obtain and maintain sufficient patent protection for Haduvio or any future product candidate and th disease indications for which we are developing or may in the future develop Haduvio or any other product candidate or if the scope of the patent protection is not sufficiently broad, competitors could develop and commercialize product

similar or identical to such product candidate and our ability to successfully commercialize such product candidate ma be adversely affected.

- The number of shares of common stock underlying our outstanding warrants is significant in relation to our currently outstanding common stock, which could have a negative effect on the market price of our common stock and make it more difficult for us to raise funds through future equity financings.

Table of Contents

PART I

Item 1. Business.

Overview

We are a clinical-stage biopharmaceutical company focused on the development and commercialization of the investigational therapy Haduvio (oral nalbuphine ER) for the treatment of chronic cough in adults with idiopathic pulmonary fibrosis, or IPF, and other refractory chronic cough, indications, and for the treatment of prurigo nodularis.or RCC.

Haduvio is an oral extended-release formulation of nalbuphine. Nalbuphine is a mixed κ-opioid receptor agonist and μ-opioid receptor antagonist that has been approved and marketed as an injectable for pain indications for more than 20 years in the U.S. and Europe. The κ- and μ-opioid receptors are known to be critical mediators of cough and itch. Nalbuphine's mechanism of action also mitigates the risk of abuse associated with μ-opioid agonists because it antagonizes, or blocks, the μ-opioid receptor. Haduvio's dual mechanism of action targets opioid receptors located in both the central and peripheral nervous systems, each of which plays a role in modulating cough and the sensation of itch. We believe this makes Haduvio a promising potential therapy for the treatment of chronic cough in IPF and RCC.

IPF To date, we have dosed over 1,100 patients with different doses of Haduvio, including healthy volunteers, patients with hepatic impairment, and patients with chronic, serious diseases such as uremic pruritus, prurigo nodularis and chronic

cough in IPF.

Chronic Cough Programs. in IPF Program. IPF is a rare, chronic, progressive lung disease, characterized by scarring and thickening of lung tissue leading to an irreversible loss of lung function and reduced life expectancy. Most patients diagnosed with IPF suffer from a dry, non-productive chronic cough that interrupts their daily living and contributes to poor quality of life. Chronic coughing can have a debilitating physical and psychosocial burden, exacerbate concomitant respiratory disease, cause loss of sleep and reduce mobility. Cough is may be an independent predictor of disease progression in IPF, and therefore we believe cough may contribute to the progression of the underlying disease.

Approximately 140,000 adults in the U.S. and greater than 1 million adults worldwide are believed to have IPF. In addition, up to 85% of IPF patients are reported to suffer from chronic cough. These patients can cough up to 1,500 times per day. There are no approved therapies for the treatment of chronic cough in patients with IPF.

In September 2022, we announced positive data from the full set of subjects patients in our Phase 2 clinical trial of Haduvio for the treatment of chronic cough in adults with IPF, which we refer to as the Phase 2 CANAL trial. The Phase 2 CANAL trial was a randomized, double-blind, placebo controlled, two-treatment, two-period, crossover study that was designed to evaluate the efficacy, safety, tolerability and dosing of Haduvio for chronic cough in adults with IPF that we conducted at multiple sites in the United Kingdom. In total, we enrolled 38 subjects 42 patients in the study. study received Haduvio. In the Phase 2 CANAL trial, Haduvio demonstrated statistically significant results for the primary efficacy endpoint of daytime cough frequency reduction ($p<0.0001$) and for key secondary endpoints on patient and clinician reported outcomes. The safety results of the trial were generally consistent with the known safety profile of Haduvio from previous trials in other patient populations.

In December 2023, we initiated our Phase 2b CORAL clinical trial, which is a dose-ranging study evaluating the efficacy, safety and tolerability of Haduvio for chronic cough in IPF. This trial is expected to be conducted at multiple sites in up to 11 countries and uses a randomized, double-blind, placebo-controlled, parallel-arm design, which evaluates three doses of Haduvio over six weeks as compared to placebo. The primary efficacy endpoint for the trial is the relative change in 24-hour cough frequency at the end of week six versus baseline for Haduvio compared to placebo, as measured via an objective cough monitor. We expect the trial to enroll approximately 160 patients. The protocol for the Phase 2b CORAL clinical trial provides for a sample size re-estimation, or SSRE, analysis once approximately 50% of the patients in the trial are evaluable for the primary endpoint. The SSRE is expected to occur in the second half of 2024, and topline data from the full trial are expected to be available in the first half of 2025 assuming there are no adjustments made to the sample size.

We are in discussions with expect to have an active investigational new drug application, or IND, for a Phase 1b clinical trial to evaluate the U.S. Food and Drug Administration, or FDA, regarding the design of the next clinical trials effect of Haduvio for the treatment of chronic cough on respiratory physiology in adult patients with IPF. We expect IPF of varying disease severity in the objectives first half of 2024. The objective for the next trials will be to determine the dose response and select a dose for the next study as well as this clinical trial is to further characterize the safety of Haduvio in this specific patient population. Subject to agreement with the U.S. Food and Drug Administration, or FDA, and other international regulatory authorities, we intend to initiate these trials this trial in 2024.

RCC Program. RCC affects up to 10% of the adult population and is defined as a persistent cough lasting more than eight weeks, despite treatment for an underlying condition. The RCC population is generally considered to also include those with unexplained chronic cough where no cough-associated conditions can be identified. RCC is related to biological changes in the second half central and peripheral nervous systems that lower the threshold of 2023. We will need the cough reflex. It is highly disruptive and accompanied by a wide range of complications, ranging from urinary incontinence in females to submit an IND sleep disruption and

---

social embarrassment that causes significant social and economic burden for Haduvio before proceeding with our planned trials patients and those around them. When a cause for chronic RCC is identifiable, it is most commonly asthma, gastroesophageal reflux disease, or GERD, non-asthmatic eosinophilic bronchitis, and upper airway cough in adults with IPF at sites syndrome or post-nasal drip. There are no approved therapies for RCC in the United States. We also plan to develop

In November 2023, we initiated our Phase 2a clinical trial of Haduvio for additional chronic cough indications, RCC, which we expect will commence initially with refer to as the Phase 2a RIVER trial. The Phase 2a RIVER trial is a Phase 2 clinical trial randomized, double-blind, placebo-controlled, two-treatment, two-period, crossover study that is designed to evaluate the efficacy, safety, tolerability and dosing of Haduvio for the treatment of refractory chronic cough, which we expect to initiate in the third quarter of 2023 RCC. We are conducting this trial at multiple sites in the U.K. United Kingdom and Canada. The trial was designed to enroll approximately 60 adult patients. The primary endpoint of the study is a mean change in 24-hour cough frequency using an objective cough monitor in the overall population. Patients are randomized with a 1:1 stratification between those with 10-19 coughs/hour (moderate 24-hour cough frequency) and those with at least 20 coughs/hour (high 24-hour cough frequency). The trial will also explore secondary endpoints, including patient reported outcome measures for cough frequency and severity. We expect to report topline efficacy and safety data in the second half of 2024.

Human Abuse Potential. We initiated a human abuse potential, or HAP, study in the fourth quarter of 2022 to compare the abuse potential of oral nalbuphine to intravenous, or IV, butorphanol. The injectable version of nalbuphine is currently unscheduled in the U.S. by the Drug Enforcement Agency. The study follows a randomized, double-blind, active and placebo-controlled five way crossover design. The study is being conducted in two parts. The first part of the study characterized various IV butorphanol doses in order to select a dose to be studied. The second part of the study is designed to utilize the selected dose and compare oral nalbuphine relative to IV butorphanol using the study metrics. We have completed the first part of the study. The FDA requested that we submit the data from the first part of the study in

support of our IV butorphanol dose selection for their review and comment prior to commencing the second part of the study. We submitted this data to the FDA and the FDA agreed with the selected dose for IV butorphanol. We initiated dosing in the second part of the study in January 2024, and, as of March 11, 2024, the study was over 50% percent enrolled. We expect to report topline data from the study in the second half of 2024.

Prurigo Nodularis. Nodularis Program. Prurigo nodularis is an intensely pruritic dermatologic condition that constitutes a distinct dermatologic diagnosis. The core symptoms and criteria for diagnosis of prurigo nodularis are chronic pruritus. Chronic pruritus, defined as itching lasting longer than six weeks, causes a number of physical and psychological issues that can substantially impact patients' daily well-being. The urge to scratch can be unbearable and the act of scratching can remove layers of skin and break the skin barrier, leading to bleeding and scarring and increasing the risk of infection. Chronic pruritus can also lead to trouble sleeping, resulting in loss of work productivity and increased anxiety and depression as patients struggle to maintain self-control. Chronic pruritus is a hallmark of many dermatologic and systemic diseases and is the predominant reason that patients with these diseases experience so much discomfort. A report published in the Journal of the American Academy of Dermatology estimated that up to 26% of the worldwide population will suffer from chronic pruritus at some point in their lives. According to the Global Pruritus Therapeutic Market Research Report issued in 2020, the market for pruritus therapeutics was $12.9 billion in 2020 and is expected to grow to $19.9 billion in 2026. Haduvio's dual mechanism

We have a development program for the use of action targets opioid receptors located in both the central and peripheral nervous systems, each of which plays a role in modulating the sensation of itch. We believe this makes Haduvio a promising potential therapy for the treatment of chronic pruritus conditions.

---

prurigo nodularis. In June 2022, we reported positive results in our Phase 2b/3 clinical trial of Haduvio in patients with prurigo nodularis, which we refer to as the Phase 2b/3 PRISM trial. The Phase 2b/3 PRISM trial was a randomized, double-blind, placebo controlled, two-arm treatment study that was designed to evaluate the safety and efficacy of Haduvio in patients with prurigo nodularis in the United States and Europe. In total we enrolled 353 subjects patients in the study. In the Phase 2b/3 PRISM trial, Haduvio demonstrated statistically significant results on the primary and all three key secondary endpoints. The safety results of the trial were generally consistent with the known safety profile of Haduvio from previous trials in other patient populations.

We In October 2023, we reported the preliminary analysis of the 52-week data from the open-label extension portion of the Phase 2b/3 PRISM trial. Following the completion of the initial 14-week portion of the trial, patients were eligible to enroll into an additional 38-week open-label extension period during which all participants received Haduvio 162mg twice a day (BID). Post hoc analyses demonstrated continued reduction in mean Worst Itch Numerical Rating Scale for those participants who remained on Haduvio through 52 weeks. 151 patients completed the open-label extension portion of our the trial, adding to the safety database for Haduvio. The safety data were generally consistent with the safety profile of Haduvio observed in the 14-week portion of the Phase 2b/3 PRISM trial and previous trials of Haduvio. Adverse events reported with a frequency greater than five percent in the first quarter 38-week open-label period included nausea, dizziness, vomiting, fatigue, and somnolence. Study discontinuation due to treatment-related adverse events occurred in

13% of 2023 patients during the 38-week open-label period, and are analyzing the results. serious adverse events, or SAEs, were reported for 13 patients, although only two of these events were considered potentially treatment related.

We expect that we will need to conduct an additional Phase 3 clinical trial to support the submission of a new drug application, or NDA, to the FDA, a marketing authorization application, or MAA, to the European Medicines Agency, or

---

EMA and an a MAA to the Medicines and Healthcare Products Regulatory Agency in the United Kingdom, or MHRA, for Haduvio for the treatment of prurigo nodularis, and plan to request an end of Phase 2 meeting with the FDA in 2023. FDA. Following discussions with the FDA and other regulatory authorities, we plan to determine next steps with respect to our prurigo nodularis program, including with respect to the conduct of any future Phase 3 clinical trial. We are exploring entering may seek to enter into a strategic collaboration for the continued development of this program.

Prior to commencing our Phase 2b/3 PRISM trial, we had completed clinical trials in two distinct and serious pruritic conditions, uremic pruritus and prurigo nodularis, with over 400 subjects patients treated with different doses of Haduvio in these trials. Uremic pruritus is a pruritic condition occurring in patients with chronic kidney disease typically receiving dialysis.

Our Strategy

We are focused on the development and commercialization of Haduvio for the treatment of chronic cough in adults with IPF and other chronic cough indications, and for the treatment of prurigo nodularis. RCC. The key elements of our strategy are:

- ***Complete the clinical development of Haduvio for the treatment of chronic cough associated with in IPF.*** In September 2022, December 2023, we announced initiated our Phase 2b CORAL clinical trial of Haduvio for chronic cough in IPF. This Phase 2b clinical trial builds on the positive data results from our the Phase 2 CANAL trial. We are clinical trial, which demonstrated a statistically significant reduction in discussions with the FDA daytime cough frequency by 75.1%, a 52.5% difference from placebo ($p<0.0001$). This trial is expected to be conducted at multiple sites in up to 11 countries and other international regulatory authorities regarding the uses a randomized, double-blind, placebo-controlled, parallel-arm design, of the next clinical trials which evaluates three doses of Haduvio for the treatment of chronic cough in adult patients with IPF. over six weeks as compared to placebo. We expect the objectives trial to enroll approximately 160 patients and to report topline data in the first half of 2025, assuming there are no adjustments made to the sample size. We expect to have an active IND for our planned Phase 1b clinical trial to evaluate the next trials will be to determine effect of Haduvio on respiratory physiology in patients with IPF of varying disease severity in the dose response and select a dose first half of

2024. The objective for the next study as well as this clinical trial is to further characterize the safety of Haduvio in this specific patient population. Subject to agreement with the FDA, and other international regulatory authorities, we intend to initiate these trials this trial in the second half of 2023. 2024.

- ***Develop Complete the clinical development of Haduvio for the treatment of additional chronic cough indications. RCC.*** We also plan to develop Haduvio for additional chronic cough indications, which In November 2023, we expect will commence initially with a initiated our Phase 2 2a RIVER clinical trial of Haduvio for the treatment of refractory chronic cough, which we expect RCC. We are conducting the Phase 2a RIVER clinical trial of Haduvio to initiate evaluate the safety and make an initial assessment of its efficacy in patients with RCC. We are conducting this trial in the third quarter United Kingdom and Canada. This trial uses a randomized, double-blind, placebo-controlled, two treatment period crossover design, which studies escalating doses of 2023 at sites Haduvio over three weeks as compared to placebo. The primary endpoint is a mean change in cough frequency using an objective cough monitor. We expect the trial to enroll approximately 60 patients and to report topline data in the U.K. second half of 2024.
- ***Determine next steps with respect to our prurigo nodularis program.*** In June 2022, we reported positive results in our Phase 2b/3 PRISM trial. We completed the open-label extension portion of the Phase 2b/3 PRISM trial in the first quarter of 2023 and are analyzing 2023. Haduvio was well-tolerated in the results. open label extension portion. Post hoc analyses demonstrated continued reduction in mean WI-NRS for those participants who remained on Haduvio through 52 weeks. We expect that we will need to conduct an additional Phase 3 clinical trial to support the submission of a an NDA to the FDA, a an MAA to the EMA and a an MAA to the MHRA for Haduvio for the treatment of prurigo nodularis, and plan to request an end of Phase 2 meeting with the FDA in 2023. FDA. Following discussions with the FDA and other regulatory authorities, we plan to determine next steps with respect to our prurigo nodularis program, including with respect to the conduct of any future Phase 3 clinical trial. We are exploring entering may seek to enter into a strategic collaboration for the continued development of this program.
- ***Maximize the commercial potential of Haduvio.*** We have retained worldwide commercial rights for Haduvio. If Haduvio receives marketing approval from the FDA for chronic cough in adults with IPF, we plan to market and commercialize Haduvio in the U.S. with our own focused, specialty sales organization targeting pulmonologists who specialize in IPF. We would not plan to market and commercialize If Haduvio receives marketing approval from the FDA for other larger chronic conditions, such as refractory chronic cough RCC or prurigo nodularis. Instead, nodularis, we would may plan to market and commercialize Haduvio in the U.S. with our own focused, specialty sales organization, or seek to enter into a strategic alliance for commercialization for such indication or indications. We also expect to utilize a variety of collaboration, distribution and other marketing arrangements with one or more third parties to commercialize Haduvio outside the U.S.

Nalbuphine Mechanistic Rationale

Nalbuphine is a mixed κ-opioid receptor agonist and μ-opioid receptor antagonist. Drugs targeting opioid receptors have been studied for decades and the biology and pharmacology of these receptors are well-understood. There are three

types of opioid receptors, mu (“μ”), kappa (“κ”) and delta (“δ”), which are expressed in varying concentrations in many

different tissues, including the central and peripheral nervous systems, airway and lung tissue, circulating immune and inflammatory cells and the skin.

Modulation of opioid receptors, either naturally or with drugs, results in multiple signaling actions at the cellular level. The receptor dynamics are complex and receptor signaling differs depending on whether the receptor is being exposed to an agonist or antagonist opioid drug. Agonists activate the receptors to which they bind, and antagonists bind to receptors, and can block the activity of agonists. In addition, opioid drugs of the same class may have different effects depending on their pharmacological properties.

In addition to the individual cellular dynamics, published research also supports the phenomena of network interaction dynamics, where activation of one type of opioid receptor type at one anatomical location can influence the activity of a different type of opiate receptor located at a different anatomical location. For example, published research has shown evidence of signaling between cell groups where κ-receptor activation on specific cells can antagonize μ-opioid receptor activation on other cells. As a result of these apparent network interaction dynamics between the κ- and μ-opioid receptors, we believe that simultaneously modulating both κ- and μ-opioid receptors with a single drug offers significant therapeutic potential in diseases that are mediated through these receptors.

Published research suggests that in certain diseases the concentration and expression of opioid receptors is different for people with the disease as compared to healthy individuals. For example, published research has shown that human skin tissue samples from patients with prurigo nodularis show a down regulation of μ-opioid receptor expression as compared to normal skin. We believe these differences in opioid receptor concentration and expression between healthy individuals and people with disease suggest that opioid drugs targeting these receptors have the potential to offer therapeutic benefit to people suffering from these diseases.

3

As shown in the diagram below, κ- and μ-opioid receptors are naturally concentrated in several areas of the body, including in the brain, brain stem, spinal cord, peripheral nerves, lungs and skin, which are the areas of the body involved in the physiology of chronic cough and chronic pruritus.

img23710298_0.jpg

With respect to cough, κ- and μ-opioid receptors in the brain stem, lungs and the peripheral lung nerves are believed to be involved in mediating respiration and the cough reflex. While there are no approved opioid therapeutics for

suppression of cough in humans, μ-agonist opioids have been used clinically to suppress cough. In addition, the mixed κ-agonist and μ-partial agonist butorphanol is approved and marketed for animals in a veterinary injection and tablet formulation for the relief of chronic non-productive cough and has been found to be 15 to 20 times more active in suppressing cough than either codeine or dextromethorphan. Further, in clinical trials, nalbuphine has demonstrated suppression of cough in fentanyl-induced cough during anesthetic induction in patients.

With respect to pruritus, the sensation of itch and the urge to scratch are known to be mediated by κ- and μ-opioid receptor expression in the reward centers of the brain as well as the spinal cord, skin and peripheral nervous system. Published clinical trials of the κ- agonist nalfurafine have demonstrated effectiveness in reducing uremic pruritus and pruritus secondary to chronic hepatic disease. Nalfurafine is approved and marketed in Japan for both conditions. Korsuva, a selective κ- agonist, has also received approval from the FDA in reducing uremic pruritus in hemodialysis patients. In addition, a number of published clinical trials have reported on the effectiveness of the μ-antagonist naltrexone in reducing pruritus related to hepatic disease and pruritus related to prurigo nodularis.

Haduvio

Haduvio is an oral extended-release formulation of nalbuphine, a small molecule and a member of the opioid agonist-antagonist class of drugs. Nalbuphine acts as an agonist at the opioid κ-receptor while competitively antagonizing the μ-opioid receptor. Nalbuphine is a marketed drug currently available only as nalbuphine hydrochloride for injection, a generic equivalent to Nubain, which has been approved in the U.S. and Europe for use in the relief of moderate to severe pain for

4

more than 20 years. Nalbuphine is not currently classified as a controlled substance in the U.S. or Europe and is not commercially available in an oral dosage form.

We have leveraged the known mechanism and proven biological activity of nalbuphine in pain to expedite the clinical development of Haduvio. We have also drawn on the safety and tolerability data from eight prior clinical trials of Haduvio conducted by Penwest Pharmaceuticals Co., or Penwest, for which we have licensed rights from Endo Pharmaceuticals Inc. (which acquired Penwest) to Haduvio, including two Phase 2 clinical trials of Haduvio for the treatment of pain, to support our clinical development efforts.

Our Haduvio Development Programs

Chronic Cough in Idiopathic Pulmonary Fibrosis IPF Program

Overview

IPF is a rare, chronic, progressive lung disease, characterized by scarring and thickening of lung tissue leading to an irreversible loss of lung function and reduced life expectancy. Most patients diagnosed with IPF suffer from a dry, non-productive chronic cough that interrupts their daily living and contributes to poor quality of life. Chronic coughing can have a debilitating physical and psychosocial burden, exacerbate concomitant respiratory disease, cause loss of sleep and reduce mobility. Cough is an independent predictor of disease progression in IPF, and therefore we believe cough may contribute to the progression of the underlying disease.

Approximately 140,000 adults in the U.S. and greater than 1 million adults worldwide are believed to have IPF. In addition, up to 85% of IPF patients are reported to suffer from chronic cough. These patients can cough up to 1,500 times per day and the urge to cough cannot be relieved by coughing. This severe coughing can lead to other morbidities. There are no approved therapies for the treatment of chronic cough in patients suffering with IPF.

The opioid class of drugs has demonstrated the ability to suppress cough and is used in the clinical management of cough. There is also preclinical and clinical evidence that mixed agonist-antagonist drugs can also be effective in treating cough.

Clinical Development

We have conducted a Phase 2 clinical trial of Haduvio for chronic cough in IPF. Following completion of the Phase 2 clinical trial described below, we had discussions with the FDA and other international regulatory authorities regarding the designs of the next clinical trials of Haduvio for the treatment of chronic cough in IPF. Based on these discussions and the results of our Phase 2 chronic cough in IPF trial, in December 2023, we initiated our Phase 2b CORAL trial of Haduvio for chronic cough in IPF. Subject to agreement with the FDA and other international regulatory authorities, we also intend to initiate a Phase 1b respiratory physiology trial of Haduvio in 2024.

Ongoing Phase 2b CORAL Clinical Trial

The Phase 2b CORAL clinical trial is a double-blind, randomized, placebo-controlled, parallel-arm trial evaluating three doses of Haduvio (27mg, 54mg and 108mg twice daily) against placebo in IPF patients with chronic cough. This trial is expected to be conducted at multiple sites in up to 11 countries. Approximately 160 IPF patients with chronic cough are expected to be randomized 1:1:1:1 to one of the three Haduvio doses or placebo for a period of six weeks, which includes

---

an initial two-week titration to the target dose followed by four weeks of fixed dose administration. The primary efficacy endpoint for the trial is the relative change in 24-hour cough frequency at the end of week six versus baseline for Haduvio

compared to placebo, as measured via an objective cough monitor. The trial will also explore secondary endpoints, including patient reported outcome measures for cough, dyspnea, and quality of life. The protocol for the Phase 2b CORAL clinical trial provides for an SSRE analysis once approximately 50% of the patients in the trial are evaluable for the primary endpoint. The SSRE is expected to occur in the second half of 2024, and topline data from the full trial are expected to be available in the first half of 2025 assuming there are no adjustments made to the sample size.

Phase 1b Respiratory Physiology Clinical Trial

We expect to have an active IND for our planned Phase 1b clinical trial to evaluate the effect of Haduvio on respiratory physiology in patients with IPF of varying disease severity in the first half of 2024. The objective for this clinical trial is to further characterize the safety of Haduvio in this specific patient population. Subject to agreement with the FDA and other international regulatory authorities, we intend to initiate this trial in 2024.

Next Steps

We expect that we will need to conduct a Phase 3 program to support the submission of an NDA to the FDA, an MAA to the EMA, and an MAA to the MHRA for Haduvio for the treatment of chronic cough in IPF, and subject to the results of the Phase 2b CORAL clinical trial and the planned Phase 1b trial, expect to request an end of Phase 2 meeting with the FDA following the Phase 2b CORAL trial in 2025. Following discussions with the FDA and other regulatory authorities, we plan to determine next steps with respect to our chronic cough in IPF program, including with respect to the conduct of any future Phase 3 clinical trials.

Phase 2 CANAL Clinical Trial

In September 2022, we announced positive data from our Phase 2 CANAL trial. The Phase 2 CANAL trial was a randomized, double-blind, placebo controlled, placebo-controlled, two-treatment, two-period, crossover study that was designed to evaluate the efficacy, safety, tolerability and dosing of Haduvio for chronic cough in adults with IPF that we conducted at multiple sites in the United Kingdom. Patients were randomized into one of two treatment arms. The patients in the first treatment arm received Haduvio for three weeks, which period was followed by a two-week washout period and then a three-week treatment period during which they received placebo. The patients in the second treatment arm received placebo during the first three-week treatment period, followed by a two-week washout period, then received Haduvio during the second three-week treatment period. During the active treatment periods, Haduvio was studied over a dosing range starting at 27 mg once daily and titrated in steps to 162 mg twice daily. The primary efficacy endpoint of the trial was mean percent change in daytime cough frequency as measured by a cough monitor as compared in the Haduvio treatment periods and the placebo treatment periods. Secondary endpoints in the trial included assessments of fatigue, dyspnea or shortness of breath and cough frequency and severity.

In total, we enrolled 38 subjects 42 patients in the trial. trial received Haduvio. In the full subject data set, Haduvio demonstrated statistically significant results for the primary efficacy endpoint of daytime cough frequency reduction ($p<0.0001$) and for key secondary endpoints on patient and clinician reported outcomes. The trial results comparing subjects patients randomized to Haduvio or placebo showed that:

- On the primary efficacy endpoint, Haduvio subjects patients had a 75.1% reduction in daytime cough frequency at of treatment period vs. study baseline compared to placebo subjects patients who had a 22.6% reduction, a 52.5%

placebo-adjusted change (p<0.0001);

- Haduvio subjects patients had a 76.1% reduction in 24-hour cough frequency at end of treatment period vs. study baseline compared to placebo subjects patients who had a 25.3% reduction, a 50.8% placebo-adjusted change (p<0.0001);
- In a post-hoc analysis, 97% of Haduvio subjects patients had at least a 30% reduction in 24-hour cough frequency compared to 35% of placebo subjects, patients, signifying a clinically meaningful reduction in cough (p<0.0001);
- Subjects Patients on Haduvio experienced a statistically significant improvement as measured by their patient reported outcomes compared to placebo over the 3-week three-week treatment period in the EXACT2: Cough Frequency Score (p=0.001) and Cough Severity Numerical Rating Scale (p=0.0001); and

---

- Based on the Clinical Global Impression of Change rating measuring clinicians' view of change since the start of th trial, 62% of Haduvio subjects patients improved vs. baseline compared to 19% of placebo subjects patients (p=0.0

The safety results of the trial were generally consistent with the known safety profile of Haduvio from previous trials in other patient populations. There were two serious adverse events SAEs reported during the trial, neither of which was considered by the

---

investigator to be treatment related. Adverse events most commonly observed during the trial were nausea, fatigue, constipation, dizziness, somnolence, vomiting, headache, anxiety and depression.

Next Steps RCC Program

We are in discussions with the FDA and other international regulatory authorities regarding the design Overview

RCC affects up to 10% of the next clinical trials of Haduvio adult population and is defined as a persistent cough lasting more than eight weeks, despite treatment for the treatment of chronic cough in adult patients with IPF. We expect the objectives for the next trials will be an underlying condition. RCC is related to determine the dose response and select a dose for the next study as well as to further characterize the safety of Haduvio in this specific patient population. Subject to agreement with the FDA, and other international regulatory authorities, we intend to initiate these trials biological changes in the second half central and peripheral nervous systems that lower the threshold of 2023. We will need the cough reflex. It is highly disruptive and accompanied by a wide range of complications, ranging from urinary incontinence in females to submit an IND sleep disruption and social embarrassment that causes significant social and economic burden for Haduvio before proceeding with our planned trials patients and those around them. The most common causes of RCC are asthma,

GERD, non-asthmatic eosinophilic bronchitis, and upper airway cough syndrome or post-nasal drip, but there are also many cases of RCC in which no cough-associated conditions can be identified. There are no approved therapies for chronic cough in adults with IPF at sites RCC in the United States.

Clinical Development

We also plan to develop are currently conducting our Phase 2a RIVER clinical trial evaluating Haduvio for additional in RCC patients, which we initiated in November 2023.

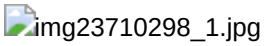
The Phase 2a RIVER trial is a double-blind, randomized, placebo-controlled, two period crossover study evaluating the safety and efficacy of Haduvio in reducing chronic cough indications, which we expect will commence initially in RCC patients. Approximately 60 RCC patients are expected to be randomized with a Phase 2 clinical trial of 1:1 stratification between those with 10-19 coughs/hour (moderate 24-hour cough frequency) and those with at least 20 coughs/hour (high 24-hour cough frequency). Each treatment period will last 21 days, separated by a 21-day washout period, and patients on Haduvio will have the dose titrated from 27 mg once a day (QD) up to 108 mg twice a day (BID) across the 21-day dosing period. The primary efficacy endpoint for the trial is the relative change in 24-hour cough frequency at day 21 from treatment of refractory chronic period baseline for Haduvio compared to placebo, as measured via an objective cough which we expect to initiate in the third quarter of 2023 at sites in the U.K. monitor. The study will also explore secondary endpoints, including patient reported outcome measures for cough frequency and severity.

Prurigo Nodularis Program

Overview

Prurigo nodularis is an intensely pruritic dermatologic condition that constitutes a distinct dermatologic diagnosis. The core symptoms and criteria for diagnosis of prurigo nodularis are chronic pruritus, a history and/or signs of repeated scratching, and the presence of multiple pruriginous lesions. The presence and persistence of these pruriginous lesions are hallmarks of prurigo nodularis and aid in its diagnosis. These lesions are generally symmetrically distributed, intensely itchy papules, nodules or plaques, which may be associated with excoriations and ulcerations. As illustrated below, prurigo nodularis can arise from itch caused by a number of pre-existing conditions, with the initial scratching beginning a vicious itch-scratch cycle that results in the nodules that are characteristic of the distinct and separate disease of prurigo nodularis.

The pruritus associated with prurigo nodularis is generally considered to be one of the most severe and treatment-resistant forms of pruritus. In a retrospective study of 108 prurigo nodularis patients published in 2013 in the Journal of the European Academy of Dermatology and Venereology, patients rating their most severe itch over the prior 24 hours on the WI-NRS reported a median Worst Itch Numerical Rating Scale, or WI-NRS, score of 8 eight and a mean and median duration of prurigo nodularis of 77.5 and 36 months, respectively. As illustrated in the diagram below, the WI-NRS is a patient-reported assessment on an 11-point scale from 0 zero to 10 of the severity of the worst itch experienced in the last 24 hours, and scores of 7 seven or more are considered to indicate severe itch.



Patients with prurigo nodularis also typically experience a significant negative impact on their overall quality of life, including severe negative impacts on their confidence at work and in social activities. In a natural history study in 593 patients with prurigo nodularis at the Itch Center, University of Münster in Germany, it was shown that all of the patients in

---

the study had a severe impairment of quality of life, as measured by the Dermatology Life Quality Index, or DLQI, a specific validated quality-of-life measurement that has been used in many different skin condition trials. With increasing intensity of pruritus, the quality of life worsened and DLQI values increased.

We believe there are approximately 300,000 prurigo nodularis patients in the U.S. and approximately 430,000 additional prurigo nodularis patients outside the U.S. Treatment of prurigo nodularis typically involves a multifaceted approach to treat the lesions and reduce pruritus. Therapies may include corticosteroids and other immunosuppressive or anti-inflammatory treatments, phototherapy and drugs such as gabapentin and Lyrica (pregabalin), prescription medicines

---

approved for the treatment of seizures and neuropathic pain, and Dupixent (dupilumab), an injectable prescription medicine, which was approved by the FDA for the treatment of prurigo nodularis in September 2022.

Clinical Development

We have conducted a Phase 2 clinical trial and an open-label extension study of Haduvio in pruritus in patients with prurigo nodularis and our a Phase 2b/3 PRISM clinical trial for Haduvio for the treatment of prurigo nodularis, including the and an open-label extension portion study of the trial. Haduvio in patients with prurigo nodularis.

Phase 2b/3 PRISM Clinical Trial

In June 2022, we reported positive results in our Phase 2b/3 PRISM trial evaluating the safety and efficacy of Haduvio as compared to placebo in patients with pruritus associated with prurigo nodularis. The trial was a multicenter, randomized, double-blind trial conducted at approximately 70 sites in the U.S. and Europe. The trial enrolled a total of 353 adult patients who had prurigo nodularis. The patients were randomized across two treatment arms: either 162 mg of Haduvio or placebo, each administered twice daily. There were two dosing periods in the trial, both of which were blinded: an initial two-week titration period during which patients received gradually increasing doses of Haduvio or placebo, reaching the final assigned dose on day 15; followed by a 12-week 12 week fixed-dosing period. Following the initial 14-week treatment

period, subjects patients continued into another two-week blinded titration period during which patients from the placebo arm crossed over to active drug with a standard escalating titration schedule, while patients from the Haduvio arm remained at a stable dose of 162 mg twice daily. This blinded two-week period was followed by an open label extension providing for 36 weeks of stable dosing at 162 mg twice daily of Haduvio for all participants. The open label extension will conclude concluded with a final two-week off-treatment washout and safety observation period for all patients.

The primary endpoint of the trial was the proportion of patients reporting at least a 4-point four point improvement from baseline to with respect to their worst itch at week 14 as measured by WI-NRS scores. Key secondary endpoints include the mean changes from baseline to week 14 in WI-NRS scores and ItchyQoL scores and the differences in percentage of subjects patients have a 1-category one category improvement in the percentage of pruriginous lesions with excoriations or crusts on the PAS at week 14. WI-NRS scores are patient-reported assessments on an 11-point scale from 0 zero to 10 of the severity of the worst itch experienced in the last 24 hours. ItchyQoL scores are used to measure how pruritus impacts a patient's quality of life.

Efficacy Results

In the Phase 2b/3 PRISM trial, Haduvio demonstrated statistically significant results on the primary and all three key secondary endpoints. The trial results comparing subjects patients randomized to Haduvio (n=168) or placebo (n=176) showed that:

- 25% of Haduvio subjects patients evaluated at week 14 met the primary endpoint of a 4-point four point reduction i WI-NRS from baseline compared to 14% of placebo subjects patients (p=0.0157);
- Haduvio subjects patients experienced significantly greater improvements in ItchyQoL vs. placebo (p=0.0002) at w 14, which was statistically significant across each of the three domains (symptoms, functional limitations, and emotions). ItchyQoL is used to measure how pruritus impacts a subject's quality of life;
- 55% of Haduvio subjects patients had at least a 1-category one category improvement in the 5-point five point scal their Prurigo Activity Scale (PAS) (pruriginous lesions with excoriations), vs. 38% on placebo (p=0.006) as evaluat at week 14;
- Haduvio subjects patients experienced significantly greater improvements in PROMIS sleep disturbance short form vs. placebo (p=0.0002) at week 14, which was statistically significant as early as week 6. six.

Safety Results

In the Phase 2b/3 PRISM trial, the safety results were generally consistent with the known safety profile of Haduvio from previous trials. During the double-blind titration period (weeks 1-2) one to two), treatment-emergent adverse events, or TEAE, were more common in the Haduvio-treated subjects patients (66.1%) vs. placebo-treated subjects patients (31.3%). During the 12-week fixed-dose period, the occurrence of TEAEs were generally similar between Haduvio and placebo groups (48% Haduvio, 45% placebo). Discontinuations during the 14-weeks 14 weeks of the trial were 36.9% in Haduvio-treated subjects patients vs. 19.3% in placebo-treated subjects. patients. During the 14-week double-blind portion of the Phase 2b/3 PRISM trial, eight subjects patients on Haduvio and six subjects patients on placebo experienced at least one treatment emergent Serious Adverse Event, or SAE. None of the SAEs were

considered by the investigator to be treatment-related. Adverse events most commonly observed with Haduvio were nausea, dizziness, headache, and constipation.

Open Label Open-Label Extension

We completed the an open-label extension study of our Phase 2b/3 PRISM clinical trial in the first quarter of 2023. Patients who completed the initial 14-week portion of the Phase 2b/3 PRISM clinical trial were able to enroll in the first quarter 38-week open-label extension study during which all participants received Haduvio 162mg twice a day (BID). Haduvio was well-tolerated in the open label extension study. Preliminary results from post hoc analyses demonstrated continued reduction in mean WI-NRS for those participants who remained on Haduvio through 52 weeks. Adverse events reported with a frequency greater than five percent in the 38-week open-label period included nausea, dizziness, vomiting, fatigue, and somnolence. Study discontinuation due to adverse events occurred in 13% of 2023 patients during the open-label period, and are analyzing SAEs were reported for 13 patients, although only two of these events were considered potentially treatment related. There were no deaths reported in the results. study.

Next Steps

We expect that we will need to conduct an additional Phase 3 clinical trial to support the submission of a an NDA to the FDA, a MAA to the EMA, and an MAA to the MHRA for Haduvio for the treatment of prurigo nodularis, and plan to request an end of Phase 2 meeting with the FDA in 2023. FDA. Following discussions with the FDA and other regulatory authorities, we plan to determine next steps with respect to our prurigo nodularis program, including with respect to the

8

conduct of any future Phase 3 clinical trial. We are exploring entering may seek to enter into a strategic collaboration for the continued development of this program.

Phase 2 Clinical Trial

We completed a Phase 2 clinical trial in August 2016 evaluating the safety and efficacy of Haduvio as compared to placebo in patients with pruritus associated with prurigo nodularis. The trial was a multicenter, randomized, double-blind trial conducted at eight sites in the U.S. and Europe. The trial enrolled a total of 63 adult patients who had prurigo nodularis for at least six weeks and seven-day seven day mean WI-NRS scores of at least 5, five, indicating moderate to severe pruritus. The patients were randomized across three treatment arms: either 162 mg or 81 mg of Haduvio or placebo, each administered twice daily. The baseline seven-day mean WI-NRS scores for the three treatment arms were comparable: 8.05 for the 162 mg arm, 8.46 for the 81 mg arm and 7.96 for the placebo arm.

The primary endpoint of the trial was the proportion of patients reporting at least a 30% reduction from baseline to week 10 in seven-day mean WI-NRS scores. We refer to these patients as 30% responders. Key secondary endpoints included:

- mean change in seven-day mean WI-NRS scores from baseline to week 10;
- the proportion of patients reporting at least a 50% reduction in seven-day seven day mean WI-NRS score from baseline to week 10, whom we refer to as 50% responders, which reduction was comparable to a 4-point four poin reduction in WI-NRS score, the primary efficacy endpoint for our Phase 2b/3 PRISM trial, for patients in the 162 m arm due to such patients having a mean baseline WI-NRS score of 8.05; and
- mean change from baseline to week 10 in total ItchyQoL score, a 22-question assessment using a severity scale o 1 one to 5 five that measures how pruritus affects patients' quality of life based on symptoms related to the pruritic condition, their functional limitations, their emotions and observations about their skin disease.

Efficacy Results

The following table summarizes the outcomes of the trial at week 10 for the primary endpoint and key secondary endpoints. The table below also includes results from a *post hoc* analysis of the 50 patients who completed the 10-week 10 week course of treatment, who we refer to as completers. We believe this *post hoc* analysis provides informative data as it eliminates the effects of patient discontinuations. With the small number of patients enrolled in the trial, the number of patients discontinuing treatment prior to the end of the trial had a substantial impact on the results, even though the number of discontinuations was small in absolute terms. Approximately 75% of the discontinuations in the Haduvio arms occurred in the titration period among patients who had not reached the target dose of Haduvio. During the trial, the discontinuation rate declined as enrollment progressed, which we believe was due to trial sites and investigators gaining experience with Haduvio and the trial.

Endpoint	**Haduvio 162 mg** mITT(1): n=18 Completers(2) : n=12	*p-value*(3)	**Haduvio 81 mg** mITT(1): n=22 Completers(2) : n=18	*p-value*(3)	**Placebo** mITT(1): n=22 Completers(2) : n=20
Responder Analyses					
30% responders in mITT population(4)	44 %	p=0.323	27 %	p=0.779	36 %
Post hoc analysis of 30% responders in completer population	75 %	p=0.026	33 %	p=0.723	40 %

50% responders in mITT population	33 %	p=0.083	14 %	p=0.981	18 %
Post hoc analysis of 50% responders in completer population (comparable in 162 mg arm to a 4-point reduction in WI-NRS score)	50 %	p=0.028	11 %	p=0.649	20 %

Endpoint	Haduvio 162 mg mITT(1): n=18 Completers(2) : n=12	p-value(3)	Haduvio 81mg mITT(1): n=22 Completers(2) : n=18	p-value(3)	Placebo mITT(1): n=22 Completers(2) : n=20
Other Key Analyses					
Mean change in seven-day mean WI-NRS scores in mITT population	(2.51)	p=0.083	(2.14)	p=0.354	(1.75)
Post hoc analysis of mean change in seven -day mean WI-NRS scores in completer population	(3.43)	p=0.025	(2.52)	p=0.491	(1.85)
Mean change in total ItchyQoL score in mITT population	(13.83)	p=0.022	(7.79)	p=0.373	(5.45)

(1) Represents the modified intention to treat population, which consists of all of the patients who were randomized and commenced dosing.

(2) Consists of the patients who completed the 10-week course of treatment.

(3) All p-values compare treatment group to placebo. Only the primary endpoint was powered for statistical significance.

(4) Primary endpoint of the trial.

In the trial, a significantly greater number of patients reported improvement in WI-NRS with 50% of the completers in the 162 mg arm reported at least a 50% reduction in WI-NRS score from baseline, as compared to 20% of the completers in the placebo arm (p=0.028), although this analysis was not powered for statistical significance. Importantly, the patients in the 162 mg arm had a mean baseline WI-NRS score of 8.05; therefore a 50% reduction in WI-NRS score from baseline for patients in this arm was comparable to a 4-point four point reduction in WI-NRS score, the primary efficacy endpoint of our ongoing Phase 2b/3 PRISM trial. While the primary endpoint of the trial demonstrated a numerical but not statistically significant difference in the 162 mg arm, we believe the results for the key secondary endpoint of the proportion of patients reporting at least a 50% reduction in WI-NRS score from baseline, and the *post hoc* analysis, allow us to better understand

the response of patients with prurigo nodularis to Haduvio and indicate that responders to Haduvio took the higher dose (162 mg) for longer (completers) and had a greater reduction in WI-NRS.

Safety Results

Haduvio was well tolerated in the trial. No serious adverse events, or SAEs were assessed as related to Haduvio. Two patients experienced SAEs that were assessed as unlikely to be related to Haduvio, including one patient in the Haduvio 81 mg arm of the trial whose SAEs occurred in connection with a car accident and one patient in the placebo arm with acute myeloid leukemia by bone marrow who experienced leukocytosis. The majority of treatment emergent adverse events, or TEAEs, occurred during the titration period. During the titration period, 73% of Haduvio-treated patients experienced one or more adverse events, as compared to 46% of patients receiving placebo.

The following table summarizes the most common TEAEs experienced by patients in the trial, indicating the percentage of the modified intention to treat, or mITT, population of each arm that reported each such TEAE, subdivided by the grade of the reported TEAEs. Grade refers to the severity of the TEAE, with grade 1 TEAEs generally including mild or asymptomatic conditions or clinical or diagnostic observations only, grade 2 two TEAEs generally including moderate events or minimal, local or noninvasive intervention events and grade 3 three TEAEs generally including severe or medically significant events that are not immediately life-threatening, events requiring hospitalization or prolongation of hospitalization or disabling events. There were no grade 4 four or grade 5 five TEAEs reported in the trial, which would generally include life-threatening or urgent intervention events and deaths. Patients were able to report multiple TEAEs

---

and, as a result, the percentages specified below for each arm or grade do not necessarily represent the percentage of patients in the arm that experienced any TEAE or any grade of any TEAE.

	Haduvio 162 mg (n=18)			Haduvio 81 mg (n=22)			Placebo (n=22)		
TEAE									
Grade	1	2	3	1	2	3	1	2	3
Dizziness	28%	11%	—	14%	9%	—	5%	—	—
Nausea	17%	22%	—	9%	9%	—	5%	—	—
Headache	11%	17%	—	9%	18%	—	5%	5%	—
Fatigue	11%	—	—	14%	5%	5%	—	—	—

Open Label Open-Label Extension Study

We completed a one-year open label one year open-label extension study of our Phase 2 clinical trial in patients with prurigo nodularis in July 2017. Patients who completed the Phase 2 clinical trial were able to enroll in the extension study following a safety washout period.

Haduvio was well-tolerated in the open label open-label extension study. The most frequent adverse events related to study drug were nausea and dizziness, which were reported in seven patients (19%) each, and fatigue, which was reported in six

patients (17%). There were no treatment emergent SAEs reported that were considered related to study drug and the majority of adverse events were grade 1 one or grade 2 two in severity. There were no deaths reported in the study.

Other Ongoing Haduvio Development Work

Human Abuse Liability Potential Study

We initiated a human abuse liability potential, or HAP, study in the fourth quarter of 2022 to compare the abuse potential of oral nalbuphine to IV butorphanol. The injectable version of nalbuphine is currently unscheduled in the U.S. by the Drug Enforcement Agency. The study is follows a randomized, double-blind, active and placebo-controlled 5-way five-way crossover design. The study will be is being conducted in two parts, with parts. The first part of the study characterized various IV butorphanol doses in order to select a dose to be studied. The second part of the study is designed to utilize the selected dose and compare oral nalbuphine relative to IV butorphanol using the study metrics. We have completed the first part characterizing various butorphanol doses. One of the study. The FDA requested that we submit the data from the first part of the study in support of our IV butorphanol dose will be selection for their review and comment prior to commencing the second part of the study. We submitted this data to the FDA and the FDA agreed with the selected to be studied dose for IV butorphanol. We initiated dosing in the second part of the protocol to determine the abuse potential study in January 2024, and as of oral nalbuphine relative to butorphanol. We are currently completing part one of March 11, 2024, the study and we was over 50% enrolled. We expect top-line to report topline data from the complete trial by study in the end second half of 2023. 2024.

Hepatic Impairment Study

We previously conducted a Phase 1b clinical trial in patients with chronic liver disease to evaluate the safety and pharmacokinetics, or PK, of Haduvio in this population. This trial was designed as an open label, open-label, non-randomized, parallel-group, single and multiple ascending dose pharmacokinetic PK trial in patients with mild, moderate and severe hepatic impairment. We completed the single ascending dosing portion of this trial in patients with mild, moderate and severe hepatic impairment and there were no serious adverse events SAEs reported in the trial. We intend to use the data from the hepatic impairment study to support an NDA submission for Haduvio.

We also anticipate conducting additional standard pharmacokinetic, PK, pharmacodynamic and other studies as needed to support marketing applications for regulatory approval in the U.S. and Europe.

Competition

The biopharmaceutical industry is intensely competitive and is subject to rapid and significant change. While we believe that our technology, knowledge, experience and scientific resources provide us with competitive advantages, we face potential competition from many sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies. If we are able to successfully develop and commercialize Haduvio, it would compete with existing therapies and new therapies that may become available in the future.

Chronic Cough in Idiopathic Pulmonary Fibrosis and Refractory Chronic Cough

If Haduvio is approved for the treatment of chronic cough associated with in IPF, we expect that it may compete with product candidates currently in clinical development for the treatment of chronic cough associated with in IPF, such as orvepitant, a NK1 receptor antagonist, which is being developed in a Phase 2b clinical trial by Nerre Therapeutics, and ifenprodil ME-015, a reactive oxygen species scavenger, which is being developed in by Melius Pharma, and ifenprodil, a Phase 2 clinical trial NMDA receptor antagonist, which is being developed by Algernon Pharmaceuticals. We expect that it might also compete with other product candidates currently in development or submitted for approval to the FDA for the treatment of refractory chronic cough and unexplained chronic cough by companies including Merck, Shionogi, Bellus Health, and Genentech. In addition, it is possible that product candidates currently in development for the treatment of IPF could, if approved, reduce the need for therapies to treat chronic cough associated in IPF. We expect that Haduvio might also compete with other product candidates currently in development, or submitted for approval to the FDA, for the treatment of RCC and unexplained chronic cough that might be used off-label to treat chronic cough in IPF.

RCC

If Haduvio is approved for the treatment of RCC, we expect that it may compete with product candidates currently in clinical development for the treatment of RCC, such as gefapixant, a P2X3 antagonist, which is being developed by Merck, however, in December of 2023, the FDA issued a complete response letter to Merck, which concluded that Merck's application did not meet substantial evidence of effectiveness for treating RCC and unexplained chronic cough. On December 20, 2023, Merck announced that it is reviewing the FDA's feedback to determine next steps. Other product candidates that are currently in development for the treatment of RCC include camlipixant, a P2X3 antagonist, which is being developed by GSK plc, NTX-1175, a charged sodium channel blocker, which is being developed by Nocion, GDC-6599, a TRPA1 antagonist, which is being developed by Genentech, ifenprodil, a NMDA receptor antagonist, which is being developed by Algernon Pharmaceuticals, AX-8, a TRPM8 antagonist, which is being developed by Axalbion, and GABAB PAM, a GABA agonist, which is being developed by Addex Therapeutics.

We also expect that Haduvio would compete with a number of therapeutics that are used off-label to treat chronic cough, including opioids, proton-pump inhibitors, and neuromodulators.

Prurigo Nodularis

We are developing Haduvio for the treatment of prurigo nodularis. There are many products that are used to help manage prurigo nodularis with which we expect that Haduvio would compete if it is approved in this indication. If Haduvio is approved for the treatment of prurigo nodularis, we expect that it would compete with Dupixent (dupilumab), an injectable prescription medicine which was jointly developed by Sanofi and Regeneron, which is approved in the U.S., E.U., Japan, and which was approved by the FDA China for the treatment of adults with moderate-to-severe prurigo nodularis in September 2022. Sanofi has announced its plans to make regulatory submissions around the world for this indication. nodularis. We also expect that Haduvio would compete with a number of therapeutics that are used off-label to treat prurigo nodularis, including anti-itch creams and emollients, as well as oral janus kinase, or JAK, receptor inhibitors, and oral or injectable antihistamines. Patients may also try gabapentin and Lyrica (pregabalin), which are prescription medicines approved for the treatment of seizures and neuropathic pain, naltrexone and UVB light therapy. We also expect that Haduvio might compete with product candidates currently in clinical development in this indication, including nemolizumab, an anti-interleukin-31 receptor A humanized monoclonal antibody being developed by Galderma; vixarelimab, a monoclonal antibody targeting oncostatin M receptor beta being developed by Kiniksa Pharmaceuticals; abrocitinib, an oral small molecule targeting the janus kinase 1, or JAK 1, receptor being developed by Pfizer Inc.; INCB054707, povorcitinib, an oral small molecule targeting the JAK 1 receptor being developed by Incyte; M1880C, ruxolitinib cream, a topical non-steroidal anti-inflammatory drug, or NSAID, therapy targeting the JAK 1/JAK 2 receptor being developed by Maruho; Incyte; and CDX-0159, barzolvolimab (CDX-0159), a humanized monoclonal antibody targeting the KIT receptor being developed by Celldex Therapeutics. In addition, a number of other product candidates are currently in clinical development to treat other pruritic conditions and Haduvio, if approved for the treatment of prurigo nodularis could face competition from these product candidates, including difelikefalin, an oral kappa opioid receptor agonist being developed by Cara Therapeutics that is initiating Phase 3 clinical trials for chronic pruritus in

patients with atopic dermatitis, and in Phase 2 clinical trials for chronic kidney disease, chronic liver disease and notalgia paresthetica.

Many of our competitors and potential competitors, either alone or with their strategic partners, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining marketing approvals and commercializing approved products than we do. Mergers and acquisitions in the biotechnology and pharmaceutical industries 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 companies also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials.

We expect that Haduvio, if approved for marketing, will compete on the basis of, among other things, efficacy, safety, health-economic benefit, convenience of administration and delivery, price, the level of generic competition and the availability of adequate reimbursement from government and other third-party payors.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than Haduvio. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for Haduvio, which could result in our competitors establishing a strong market position before we are able to enter the market.

License Agreements

Exclusive License Agreement with Endo Pharmaceuticals

In May 2011, we entered into an agreement with Penwest (subsequently Pharmaceuticals Co., which subsequently merged into its parent, Endo) Endo Pharmaceuticals Inc., or Endo, for an exclusive, worldwide, sublicensable license under certain patent rights and know-how controlled by Penwest Endo to develop and commercialize products incorporating nalbuphine hydrochloride in any formulation, including an extended-release formulation such as Haduvio, in all fields and for any use.

Under the license agreement, we paid Penwest Endo a minimal, non-creditable, non-refundable upfront license fee. We may also become obligated to make milestone payments to Endo of $0.3 million, which would become due upon the successful completion of the first Phase 3 clinical trial of a licensed product candidate, and $0.8 million, which would become due upon the marketing approval of a licensed product in the United States, U.S., and to pay royalties based on net sales of the licensed products by us, our affiliates and sublicensees. In addition, we are obligated to pay Endo a low-to-mid double-digit percentage of certain income we receive from sublicensees, based on the date of the definitive agreement under which the sublicense was granted.

Our royalty obligation with respect to each licensed product in each country commences upon the first commercial sale of the product in that country and extends until the later of the expiration, unenforceability or invalidation of the last valid claim of any licensed patent or application covering the licensed product in the country or the expiration of 10 years after the first commercial sale of the licensed product in the country, which period is referred to as the royalty term. Upon the expiration of the royalty term for a product in a country, we are thereafter obligated to pay a low single-digit know-how and trademark royalty.

Under the agreement, we have granted Endo a non-exclusive, royalty-free (except for pass-through payments to third parties), sublicensable license under our relevant patent rights, to use any improvement we make to Endo's controlled release technology, for any product other than the products under which we are licensed by Endo.

Both we and Endo have the right to terminate the agreement if the other party materially breaches the agreement and fails to cure the breach within specified cure periods. Endo also has the right to terminate in the event we undergo specified bankruptcy, insolvency or liquidation events, and we events. We have the right to terminate the agreement for at our convenience at any time on 180 days' notice to Endo. Additionally, if we or any of our sublicensees challenge the validity or enforceability of any licensed patent rights covering a licensed product, and that challenge is not terminated within a specified period, the agreement will immediately terminate and all licenses granted under the agreement will shall be revoked.

Upon termination of the agreement, we must transfer to Endo all regulatory filings and approvals relating to the development, manufacture or commercialization of the licensed products and all trademarks, other than our corporate trademarks, then being used in connection with the licensed products. If the agreement is terminated under certain specified circumstances, we will be deemed to have granted Endo a perpetual, royalty-free (except for pass-through payments to third parties), worldwide, exclusive, sublicensable license, under any improvements we made to the licensed know-how, and any related patent rights we have, to manufacture and commercialize the licensed products.

Manufacturing

We currently contract with third parties for the supply of nalbuphine hydrochloride drug substance and the manufacture of Haduvio tablets for clinical trials and intend to do so for clinical and commercial supply in the future. We do not own or operate facilities for the production of clinical or commercial quantities of drug substance or drug product. We currently have no plans to build our own clinical or commercial scale manufacturing capabilities. Although we rely on contract manufacturers, we have personnel with experience to oversee our relationships with contract manufacturers.

Haduvio is manufactured from readily available starting materials using established, scalable processes that do not require any special equipment or technology. Nalbuphine hydrochloride drug substance is commercially available and manufactured at production scale. Haduvio tablets are currently manufactured at a scale sufficient for use in clinical trials. Process development work is also being planned.

We believe that our current suppliers and manufacturers have the capacity to support commercial scale production of Haduvio, however we have no formal agreements with them to cover commercial production and we may seek to pursue supply or manufacturing arrangements with additional or alternative parties in the future. While we believe there are alternate sources of supply that can satisfy our clinical requirements and any future commercial requirements, replacing or adding a supplier or manufacturer could result in additional cost or delay.

Commercial Operations

We have retained worldwide commercial rights for Haduvio. If Haduvio receives marketing approval from the FDA for chronic cough in adults with IPF, we plan to market and commercialize Haduvio in the U.S. with our own focused, specialty sales organization targeting pulmonologists who specialize in IPF. We would not If Haduvio receives marketing approval from the FDA for other larger chronic conditions, such as RCC or prurigo nodularis, we may plan to market and commercialize Haduvio for other larger conditions such as refractory chronic cough in the U.S. with our own focused, specialty sales organization, or prurigo nodularis. Instead, we would plan to seek to enter into a strategic alliance for commercialization for such indication or indications. We also expect to utilize a variety of collaboration, distribution and other marketing arrangements with one or more third parties to commercialize Haduvio outside the U.S.

Intellectual Property

Our commercial success depends in part on our ability to obtain and maintain proprietary protection for Haduvio and our manufacturing and process discoveries and other know-how, to operate without infringing the proprietary rights of others and to prevent others from infringing our proprietary rights. Our policy is to seek to protect our proprietary position by, among other methods, filing U.S. and foreign patent applications related to our proprietary technology, inventions and improvements that are important to the development and implementation of our business. We also rely on trade secrets, know-how, continuing technological innovation and potential in-licensing opportunities to develop and maintain our proprietary position.

As of December 31, 2022 December 31, 2023, we owned four five U.S. patents, eight 11 foreign patents and multiple pending U.S. and foreign patent applications that include claims relating to methods of use of Haduvio. In March 2023, we received Haduvio, including a Notice of Allowance for the U.S. patent application covering the use of Haduvio for the treatment of chronic cough in IPF. The issued patents expire between 2032 and 2039 and the patent applications, if issued as patents, in the patent application for which we were issued a Notice of Allowance, would expire between 2032 and 2041.

In addition, we are party to an exclusive license agreement with Endo under which we have licensed patent rights and know-how to develop and commercialize products incorporating nalbuphine hydrochloride in any formulation, including Haduvio. As of December 31, 2022 December 31, 2023, the intellectual property in-licensed under this agreement included six U.S. patents and four foreign patents, which include granted European patent rights that have been validated in various European Union, or E.U., member states. The licensed patents from Endo include claims relating to the formulation of Haduvio. These patents expire between 2026 and 2029.

In addition, we have in-licensed three issued U.S. patents, one issued European patent, one Japanese patent, one issued Canadian patent and a pending application in the U.S. These patents and the patent application relate to the use of

nalbuphine in various movement disorders. The U.S. patents expire in 2032. The Japanese, European and Canadian patents expire in 2032.

We do not own or exclusively license any composition of matter patents for Haduvio.

The terms of individual patents depend upon the legal term for patents in the countries in which they are granted. In most countries, including the U.S., the patent term is generally 20 years from the earliest claimed filing date of a nonprovisional patent application in the applicable country. In the U.S., a patent's term may, in certain cases, be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark

Office, or USPTO, in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over a commonly owned patent or a patent naming a common inventor and having an earlier expiration date.

Similar provisions are available in the E.U. and certain other non-U.S. jurisdictions to extend the term of a patent that covers an approved drug. The expiration dates referred to above are without regard to potential patent term extension or other market exclusivity that may be available to us. However, we cannot provide any assurances that any such patent term extension of a non-U.S. patent will be obtained and, if obtained, the duration of such extension. We also protect our proprietary technology and processes, in part, by confidentiality and invention assignment agreements with our employees, consultants, scientific advisors and other contractors. These agreements may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our employees, consultants, scientific advisors or other contractors use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

Our commercial success will also depend in part on not infringing the proprietary rights of third parties. It is uncertain whether the issuance of any third-party patent would require us to alter our development or commercial strategies, alter our processes, obtain licenses or cease certain activities. Our breach of any license agreements or failure to obtain a license to proprietary rights that we may require to develop or commercialize Haduvio or any future product candidate may have a material adverse impact on us. If third parties prepare and file patent applications in the U.S. that also claim technology to which we have rights, we may have to participate in interference or derivation proceedings in the USPTO to determine priority of invention.

Government Regulation and Product Approvals

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

In the U.S., drug products are regulated under the Federal Food, Drug, and Cosmetic Act, or FDCA, and applicable implementing regulations and guidance. A company, institution, or organization which takes responsibility for the initiation and management of a clinical development program for such products, and for their regulatory approval, is typically referred to as a sponsor. The failure of a sponsor to comply with the applicable regulatory requirements at any time during the product development process, including non-clinical testing, clinical testing, the approval process or the post-approval process, may result in delays to the conduct of a study, regulatory review and approval and/or administrative or judicial sanctions.

A sponsor seeking approval to market and distribute a new drug in the U.S. generally must satisfactorily complete each of the following steps before the FDA will consider approving the product candidate:

- preclinical testing including laboratory tests, animal studies and formulation studies, which must be performed in accordance with the FDA's good laboratory practice, or GLP, regulations and standards;
- completion of the manufacture, under current Good Manufacturing Practices, or cGMP, conditions, of the drug substance and drug product that the sponsor intends to use in human clinical trials along with required analytical an stability testing;
- design of a clinical protocol and submission to the FDA of an IND for human clinical testing, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical tria may be initiated;
- performance of adequate and well-controlled human clinical trials to establish the safety potency and purity efficacy the product candidate for each proposed indication, in accordance with current good clinical practices, or GCP; cGC
- preparation and submission to the FDA of an NDA for a drug product which includes not only the results of the clinic trials, but also, detailed information on the chemistry, of manufacturing and manufacture and quality controls, or CM for the product candidate and proposed labelling for one or more proposed indication(s);
- review of the product candidate by an FDA advisory committee, where appropriate or if applicable;

14

- satisfactory completion of an FDA inspection of the manufacturing facility or facilities, including those of third parties at which the product candidate or components thereof are manufactured to assess compliance with cGMP

requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;

- satisfactory completion of any FDA audits of the non-clinical and clinical trial sites to assure compliance with GCPs cGCPs and the integrity of clinical data in support of the NDA;
- payment of user fees and securing FDA approval of the NDA to allow marketing of the new drug product; and
- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluatio and Mitigation Strategy, or REMS and the potential requirement to conduct any post-approval studies required by th FDA.

Preclinical Studies

Before a sponsor begins testing a product candidate with potential therapeutic value in humans, the product candidate enters the preclinical testing stage. Preclinical tests include laboratory evaluations of product chemistry, formulation and stability, as well as other studies to evaluate, among other things, the toxicity of the product candidate. These studies are generally referred to as IND-enabling studies. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements, including GLP regulations and standards and the United States Department of Agriculture's Animal Welfare Act, if applicable. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, and long-term toxicity studies, may continue after the IND is submitted.

The IND and IRB Processes

An IND is an exemption from the FDCA that allows an unapproved product candidate to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer such investigational product to humans. Such authorization must be secured prior to interstate shipment and administration of any product candidate that is not the subject of an approved NDA. In support of a request for an IND, sponsors must submit a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. The FDA requires a 30-day waiting period after the filing of each IND before clinical trials may begin. This waiting period is designed to allow the FDA to review the IND to determine whether human research subjects patients will be exposed to

unreasonable health risks. At any time during this 30-day period, or thereafter, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold or partial clinical hold. The FDA may also

place a hold or partial hold on a clinical study based on CMC issues involving the investigational product. In this either case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a partial clinical hold might state that a specific protocol or part of a protocol may not proceed, while other parts of a protocol or other protocols may do so. No more than 30 days after the imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following the issuance of a clinical hold or partial clinical hold, a clinical investigation may only resume once the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the investigation can proceed or recommence.

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 Once an IND all IND requirements must be met unless waived by the FDA. When a foreign clinical study is not conducted under an IND, application takes effect, the sponsor must of the IND may amend the application as needed to ensure that the study complies with certain regulatory requirements clinical investigations are conducted according to protocols included in the IND. The FDA has indicated that sponsors are expected to submit amendments for new protocols or changes to existing protocols before implementation of the respective changes. New studies may begin, however, when the sponsor has submitted the change to the FDA in order to use the study as support for an IND or application for marketing approval. Specifically, the studies must be conducted in accordance with GCP, including undergoing its review and receiving the new protocol or changes to the existing protocol have been approved by the IRB with the responsibility for review and approval by an independent ethics committee, or IEC, and seeking and receiving informed consent from subjects. The GCP requirements in the final rule encompass both ethical and data integrity standards for clinical studies. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies, as well as the quality and integrity of the resulting data.

studies. In addition to the foregoing IND requirements, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove the study at least annually. The IRB, which must operate in compliance with FDA regulations, must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. patients. An IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it

represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product candidate has been associated with unexpected serious harm to patients.

Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board, or DSMB. This group provides authorization as to whether or not a trial may

move forward at designated checkpoints based on review of available data from the study, to which only the DSMB maintains access. Suspension or termination of development during any phase of a clinical trial can occur if the DSMB determines that the participants or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made by us based on evolving business objectives and/or competitive climate.

Expanded Access to an Investigational Drug for Treatment Use

Expanded access, sometimes called “compassionate use,” is the use of investigational new drug products outside of clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options. The rules and regulations related to expanded access are intended to improve access to investigational drugs for patients who may benefit from investigational therapies. FDA regulations allow access to investigational drugs under an IND by the company or the treating physician for treatment purposes on a case-by-case basis for: individual patients (single-patient IND applications for treatment in emergency settings and non-emergency settings); intermediate-size patient populations; and larger populations for use of the drug under a treatment protocol or Treatment IND Application.

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

There is no obligation for a sponsor to make its drug products available for expanded access; however, as required by the 21st Century Cures Act, or Cures Act, passed in 2016, if a sponsor has a policy regarding how it responds to expanded access requests, it must make that policy publicly available. Sponsors are required to make such policies publicly available upon the earlier of initiation of a Phase 2 or Phase 3 study; or 15 days after the investigational drug or biologic receives designation as a breakthrough therapy, fast-track product, or regenerative medicine advanced therapy.

In addition, on May 30, 2018, the Right to Try Act was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase 1

clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a drug manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act, but the manufacturer must develop an internal policy and respond to patient requests according to that policy.

Human Clinical Trials in Support of an NDA

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

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

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

Phase 2 clinical trials are generally conducted in a limited patient population to identify possible adverse effects and safety risks, evaluate the efficacy of the product candidate for specific targeted indications and determine dose tolerance

and optimal dosage. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more costly Phase 3 clinical trials. Phase 2 clinical trials are well-controlled and closely monitored.

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

A clinical trial may combine the elements of more than one phase and the FDA often requires more than one Phase 3 trial to support marketing approval of a product candidate. A company's designation of a clinical trial as being of a particular phase is not necessarily indicative that the study will be sufficient to satisfy the FDA requirements of that phase because

this determination cannot be made until the protocol and data have been submitted to and reviewed by the FDA. Generally, pivotal trials are Phase 3 trials, but they may be Phase 2 trials if the design provides a well-controlled and reliable assessment of clinical benefit, particularly in an area of unmet medical need.

In December 2022, with passage of the Food and Drug Omnibus Reform Act, or FDORA, Congress required sponsors to develop and submit a diversity action plan for each phase Phase 3 clinical trial or any other "pivotal study" of a new drug or biological product. These plans are meant to encourage the enrollment of more diverse patient populations in late-stage clinical trials of FDA-regulated products. Specifically, action plans must include the sponsor's goals for enrollment, the underlying rationale for those goals, and an explanation of how the sponsor intends to meet them. In addition to these requirements, the legislation directs the FDA to issue new guidance on diversity action plans. In January 2024, the FDA issued draft guidance setting out its policies for the collection of race and ethnicity data in clinical trials.

In June 2023, the FDA issued draft guidance with updated recommendations for cGCPs aimed at modernizing the design and conduct of clinical trials. The updates are intended to help pave the way for more efficient clinical trials to facilitate the development of medical products. The draft guidance is adopted from the International Council for Harmonisation's recently updated E6(R3) draft guideline that was developed to enable the incorporation of rapidly developing technological and methodological innovations into the clinical trial enterprise. In addition, the FDA issued draft guidance outlining recommendations for the implementation of decentralized clinical trials.

In some cases, the FDA may approve an NDA for a product candidate but require the sponsor to conduct additional clinical trials to further assess the product candidate's safety and effectiveness after approval. Such post-approval trials are typically referred to as Phase 4 post-approval or post-marketing clinical trials. These trials are used to gain additional experience from the treatment of a larger number of patients in the intended treatment group and to further document a clinical benefit in the case of drugs approved under accelerated approval regulations. Failure to exhibit due diligence with regard to conducting Phase 4 clinical trials could result in withdrawal of FDA approval for products.

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

Finally, sponsors of clinical trials are required to register and disclose certain clinical trial information on a public registry (clinicaltrials.gov) maintained by the U.S. National Institutes of Health, or NIH. In particular, information related to the product, patient population, phase of investigation, study sites and investigators and other aspects of the clinical trial is made public as part of the registration of the clinical trial. Although the FDA has historically not enforced these reporting requirements due to the long delay of the Department of Health and Human Services, or HHS, in issuing final implementing regulations, those regulations have now been issued and the FDA has issued several Notices pre-notices for voluntary corrective action and several notices of Noncompliance to manufacturers since April 2021. The non-compliance during the past two years. While these notices of non-compliance did not result in civil monetary penalties, the failure to submit clinical trial information to clinicaltrials.gov, as required, is a prohibited act under the FDCA with violations subject to potential civil monetary penalties of up to $10,000 for each day the violation continues.

Clinical Studies Outside the United States in Support of FDA Approval

In connection with our clinical development program, we may conduct trials at sites outside the United States. When a foreign clinical study is conducted under an IND, all IND requirements must be met unless waived. When a foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with certain regulatory requirements of the FDA in order to use the study as support for an IND or application for marketing approval. Specifically, the studies must be conducted in accordance with cGCP, including undergoing review and receiving approval by an independent ethics committee and seeking and receiving informed consent from subjects. cGCP requirements encompass both ethical and data integrity standards for clinical studies. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign studies are conducted in a manner comparable to that required for IND studies.

The acceptance by the FDA of study data from clinical trials conducted outside the United States in support of U.S. approval may be subject to certain conditions or may not be accepted at all. In cases where data from foreign clinical trials are intended to serve as the sole basis for marketing approval in the U.S., the FDA will generally not approve the application on the basis of foreign data alone unless (i) the data are applicable to the U.S. population and U.S. medical practice; (ii) the trials were performed by clinical investigators of recognized competence and pursuant to cGCP regulations; and (iii) the data may be considered valid without the need for an on-site inspection by the FDA, or, if the FDA considers such inspection to be necessary, the FDA is able to validate the data through an on-site inspection or other appropriate means.

In addition, even where the foreign study data are not intended to serve as the sole basis for approval, the FDA will not accept the data as support for an application for marketing approval unless the study is well-designed and well-conducted in accordance with cGCP requirements and the FDA is able to validate the data from the study through an onsite inspection if deemed necessary. Many foreign regulatory authorities have similar approval requirements. In addition, such foreign trials are subject to the applicable local laws of the foreign jurisdictions where the trials are conducted.

Interactions with the FDA During the Clinical Development Program

Following the clearance of an IND and the commencement of clinical trials, a sponsor is given the opportunity to meet with the FDA at certain points in the clinical development program. There are five types of meetings that occur between

sponsors and the FDA. Type A meetings are those that are necessary for an otherwise stalled product development program to proceed or to address an important safety issue. Type B meetings include pre-IND and pre-NDA meetings as well as end of phase meetings such as an end of Phase 2 meeting, or EOP2 meeting. A Type C meeting is any meeting other than a Type A or Type B meeting regarding the development and review of a product. A Type D meeting is focused on a narrow set of issues and should not require input from more than three disciplines or divisions. Finally, INTERACT meetings are intended for novel products and development programs that present unique challenges in the early development of an investigational product.

The FDA has indicated that its responses, as conveyed in meeting minutes and advice letters, only constitute mere recommendations and/or advice made to a sponsor and, as such, sponsors are not bound by such recommendations and/or advice. Nonetheless, from a practical perspective, a sponsor's failure to follow the FDA's recommendations for design of a clinical program may put the program at significant risk of failure.

Pediatric Studies

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

For investigational products intended to treat a serious or life-threatening disease or condition, the FDA must, upon the request of a sponsor, meet to discuss preparation of the initial pediatric study plan or to discuss deferral or waiver of

pediatric assessments. In addition, the FDA will meet early in the development process to discuss pediatric study plans with sponsors, and the FDA must meet with sponsors by no later than the end-of-phase 1 meeting for serious or life-threatening diseases and by no later than ninety days after the FDA's receipt of the study plan.

The FDA may, on its own initiative or at the request of the sponsor, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. A deferral may be granted for several reasons, including a finding that the product or therapeutic candidate is ready for approval for use in adults before pediatric trials are complete. The law requires the FDA is required to send a PREA Non-Compliance letter to sponsors who have failed to submit their pediatric assessments required under PREA, and have failed to seek or obtain a deferral or deferral extension. Unless otherwise required by regulation, the pediatric data requirements generally do not apply to products with orphan designation, although FDA has recently taken steps to limit what it considers abuse of this statutory exemption in PREA. In May 2023, the FDA issued new draft guidance that further describes the pediatric study requirements under PREA.

Submission and Review of an NDA

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

The NDA is a vehicle through which sponsors formally propose that the FDA approve a new product for marketing and sale in the U.S. for one or more indications. Every new drug product candidate must be the subject of an approved NDA before it may be commercialized in the U.S. Under federal law, the submission of most NDAs is subject to an application user fee, which for federal fiscal year 2023 2024 is $3,242,026 $4,048,695 for an application requiring clinical data. The sponsor of an approved NDA is also subject to an annual program fee, which for federal fiscal year 2023 2024 is $393,933. $416,734. Certain exceptions and waivers are available for some of these fees, such as a waiver for certain small businesses.

Following submission of an NDA, the FDA conducts a preliminary review of the application within 60 days of receipt and must inform the sponsor at that time or before whether an application is sufficiently complete to permit substantive review. In the event that FDA determines that an application does not satisfy this standard, it will issue a Refuse to File, or RTF, determination to the sponsor. The FDA may request additional information rather than accept the application for filing. In this event, the application must be resubmitted with the requested additional information. The resubmitted application is also subject to review before the FDA accepts it for filing.

Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA reviews the application to determine, among other things, whether the proposed product is safe and effective for its intended use, whether it has an acceptable purity profile and whether the product is being manufactured in accordance with cGMP. The FDA has agreed to specified performance goals in the review process of NDAs. Under that agreement, 90% of applications seeking approval of New Molecular Entities, or NMEs, are meant to be reviewed within 10 months from the date on which

the FDA accepts the application for filing, and 90% of applications for NMEs that have been designated for “priority review” are meant to be reviewed within six months of the filing date.

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

Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP cGCP and the integrity of the data submitted in support of the application. With passage of FDORA, Congress clarified FDA’s authority to conduct inspections by expressly permitting inspection of facilities involved in the preparation, conduct, or analysis of clinical and non-clinical studies submitted to FDA as well as other persons holding study records or involved in the study process.

In addition, as a condition of approval, the FDA may require a sponsor to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product,

seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential adverse events and whether the product is an NME.

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

Expedited Review Programs

The FDA is authorized to expedite the review of NDAs in several ways. Under the Fast Track program, the sponsor of a product candidate may request the FDA to designate the product for a specific indication as a Fast Track product concurrent with or after the filing of the IND. Candidate products are eligible for Fast Track designation if they are intended

to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product candidate and the specific indication for which it is being studied. In addition to other benefits, such as the ability to have greater interactions with the FDA, the FDA may initiate review of sections of a Fast Track application before the application is complete, a process known as rolling review.

Any product candidate submitted to the FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as breakthrough therapy designation, priority review and accelerated approval.

Breakthrough Therapy designation. To qualify for the Breakthrough Therapy program, product candidates must be intended to treat a serious or life-threatening disease or condition and preliminary clinical evidence must indicate that such product candidates may demonstrate substantial improvement on one or more clinically significant endpoints over existing therapies. The FDA will seek to ensure the sponsor of a Breakthrough Therapy product candidate receives intensive guidance on an efficient drug development program, intensive involvement of senior managers and experienced staff on a proactive, collaborative and cross-disciplinary review and rolling review.

Priority Review. A product candidate is eligible for Priority Review if it treats a serious condition and, if approved, it would be a significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention compared to marketed products. The FDA aims to complete its review of Priority Review applications within six months as opposed to 10 months for standard review.

Accelerated approval. Drug or biologic products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval. Accelerated approval means that a product candidate may be approved on the basis of adequate and well controlled clinical trials establishing that the product candidate has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity and prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require that a sponsor of a drug or biologic product candidate receiving accelerated approval perform adequate and well controlled post-marketing clinical trials. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials.

With the passage of FDORA in December 2022, Congress modified certain provisions governing accelerated approval of drug and biologic products. Specifically, the new legislation authorized the FDA to: require a sponsor to have its confirmatory clinical trial underway before accelerated approval is awarded, require a sponsor of a product granted

accelerated approval to submit progress reports on its post-approval studies to FDA every six months (until the study is completed); and use expedited procedures to withdraw accelerated approval of an NDA or biologics license application, or BLA, after the confirmatory trial fails to verify the product's clinical benefit. Further, FDORA requires the agency to publish on its website "the rationale for why a post-approval study is not appropriate or necessary" whenever it decides not to require such a study upon granting accelerated approval.

Regenerative advanced therapy. With passage of the 21st Century Cures Act, or the Cures Act, in December 2016, Congress authorized the FDA to accelerate review and approval of products designated as regenerative advanced therapies. A product is eligible for this designation if it is a regenerative medicine therapy that is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product candidate has the potential to address unmet medical needs for such disease or condition. The benefits of a regenerative advanced therapy designation include early interactions with the FDA to expedite development and review, benefits available to breakthrough therapies, potential eligibility for priority review and accelerated approval based on surrogate or intermediate endpoints.

None of these expedited programs change the standards for approval but they may help expedite the development or approval process of product candidates.

The FDA's Decision on an NDA

On the basis of the FDA's evaluation of an NDA and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter, or CRL. To reach this determination, the FDA reviews an application to determine, among other things, whether the product is safe and effective for its intended use. The FDA must determine that the investigational product is effective and that its expected benefits outweigh its potential risks to patients. This "benefit-risk" assessment is informed by the extensive body of evidence about the product's safety, purity and potency in the BLA. This assessment is also informed by other factors, including: the severity of the underlying condition and how well patients' medical needs are addressed by currently available therapies; uncertainty about how the premarket clinical trial evidence will extrapolate to real-world use of the product in the post-market setting; and whether risk management tools are necessary to manage specific risks.

A CRL generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If a CRL is issued, the sponsor will have one year to respond to the deficiencies identified by the FDA, at which time the FDA can deem the application withdrawn or, in its discretion, grant the sponsor an additional six month extension to respond. For those seeking to challenge FDA's CRL decision, the agency has indicated that sponsors may request a formal hearing on the CRL or they may file a request for reconsideration or a request for a formal dispute resolution.

An approval letter, on the other hand, authorizes commercial marketing of the product with specific prescribing information for specific conditions. The FDA may limit the approved indications for use of the product. The agency may also require testing and surveillance programs to monitor the product after the initiation of commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, such as REMS, to help ensure that the benefits of the product outweigh the potential risks. REMS can include medication guides, communication plans for health care professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring and the use of patient registries. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Regulation

If regulatory approval for marketing of a product or a new indication for an existing product is obtained, the sponsor will be required to comply with all regular post-approval regulatory requirements as well as any post-approval requirements that the FDA may have imposed as part of the approval process. The sponsor will be required to report, among other things, certain adverse reactions and manufacturing problems to the FDA, provide updated safety and efficacy information and comply with requirements concerning advertising and promotional labeling requirements. Manufacturers and certain of 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 ongoing regulatory requirements, including cGMP regulations, which impose certain procedural and documentation requirements upon

---

manufacturers. Accordingly, the sponsor and its third-party manufacturers must continue to expend time, money and effort in the areas of production and quality control to maintain compliance with cGMP regulations and other regulatory requirements.

A product may also be subject to official lot release, meaning that the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release, the manufacturer must submit samples of each lot, together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer’s tests performed on the lot, to the FDA. The FDA may perform certain confirmatory tests on lots of some products before releasing the lots for distribution. Finally, the FDA will conduct laboratory research related to the safety, purity, potency and effectiveness of pharmaceutical products.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, 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 trials to assess safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

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

- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates the marketing, labeling, advertising and promotion of prescription drug products placed on the market. This regulation includes, among other things, standards and regulations for direct-to-consumer advertising, communications regarding unapproved uses, industry-sponsored scientific and educational activities, and promotional activities involving the Internet and social media. Promotional claims about a drug's safety or effectiveness are prohibited before the drug is approved. After approval, a drug product generally may not be promoted for uses that are not approved by the FDA, as reflected in the product's prescribing information. In September 2021, the FDA published final regulations which describe the types of evidence that the agency will consider in determining the intended use of a drug product.

It may be permissible, under very specific, narrow conditions, for a manufacturer to engage in non-promotional, non-misleading communication regarding off-label information, such as distributing scientific or medical journal information. Moreover, with passage of the Pre-Approval Information Exchange Act, or PIE Act, in December 2022, sponsors of products that have not been approved may proactively communicate to payors certain information about products in development to help expedite patient access upon product approval. Previously, such communications were permitted under FDA guidance but the new legislation PIE Act explicitly provides protection to sponsors who convey certain information about products in development to payors, including unapproved uses of approved products. In addition, in October 2023, the FDA published draft guidance outlining the agency's non-binding policies governing the distribution of scientific information on unapproved uses to healthcare providers. This draft guidance calls for such communications to be truthful, non-misleading, factual, and unbiased and include all information necessary for healthcare providers to interpret the strengths and weaknesses and validity and utility of the information about the unapproved use.

If a company is found to have promoted off-label uses, it may become subject to adverse public relations and administrative and judicial enforcement by the FDA, the Department of Justice, or the Office of the Inspector General of the Department of Health and Human Services, HHS, as well as state authorities. This could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that materially

restrict the manner in which a company promotes or distributes drug products. The federal government has levied large civil and criminal fines against companies for alleged improper promotion and has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, and its implementing regulations, as well as the Drug Supply Chain Security Act, or DSCA, which regulate the distribution and tracing of prescription drug samples at the federal level and set minimum standards for the regulation of distributors by the states. The PDMA, its implementing regulations and state laws limit the distribution of prescription

---

pharmaceutical product samples, and the DSCA imposes requirements to ensure accountability in distribution and to identify and remove counterfeit and other illegitimate products from the market.

Section 505(b)(2) NDAs

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

Thus, Section 505(b)(2) authorizes the FDA to approve an NDA based on safety and effectiveness data that were not developed by or for the sponsor. NDAs filed under Section 505(b)(2) may provide an alternate and potentially more expeditious pathway to FDA approval for new or improved formulations or new uses of previously approved products. If the 505(b)(2) sponsor can establish that reliance on the FDA's previous approval is scientifically appropriate, the sponsor may eliminate the need to conduct certain preclinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements to support the change from the approved product. The FDA may then approve the new drug candidate for all or some of the label indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) sponsor.

Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Hatch-Waxman Act, Congress established an abbreviated regulatory scheme authorizing the FDA to approve generic drugs that are shown to contain the same active ingredients as, and to be bioequivalent to, drugs previously approved by the FDA pursuant to NDAs.

In order for an abbreviated new drug application, or ANDA, to be approved, the FDA must find that the generic version is identical to the reference listed drug, or RLD, with respect to the active ingredients, the route of administration, the dosage form, the strength of the drug and the conditions of use of the drug. At the same time, the FDA must also determine that the generic drug is "bioequivalent" to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug." Upon approval of an ANDA, the FDA indicates whether the generic product is "therapeutically equivalent" to the RLD in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Physicians and pharmacists consider a therapeutic equivalent generic drug to be fully substitutable for the RLD.

Under the Hatch-Waxman Act, the FDA may not approve an ANDA until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity, or NCE. For the purposes of this provision, an NCE is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. This interpretation of the FDCA by the FDA was confirmed with enactment of the Ensuring Innovation Act in April 2021. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such NCE exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the sponsor may submit its application four years following the original product approval.

The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the sponsor and are essential to the approval of the application.

Hatch-Waxman Act Patent Certification and the 30-Month Stay

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the sponsor's product or an approved method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. The FDA's regulations governing patient listings were largely codified into law with enactment of the Orange Book Modernization Act in January 2021. When an ANDA sponsor files its application with the FDA, the sponsor is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA sponsor is not seeking approval. To the extent that the Section 505(b)(2) sponsor is relying on studies conducted for an already approved product, the sponsor is required to

certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA sponsor would.

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

- the required patent information has not been filed;
- the listed patent has expired;
- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; o
- the listed patent is invalid, is unenforceable or will not be infringed by the new product.

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

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

To the extent that the Section 505(b)(2) sponsor is relying on studies conducted for an already approved product, the sponsor is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA sponsor would. As a result, approval of a Section 505(b)(2) NDA can be stalled until all the listed patents claiming the referenced product have expired, until any non-patent exclusivity, such as exclusivity for obtaining approval of an NCE, listed in the Orange Book for the referenced product has expired, and, in the case of a

Paragraph IV certification and subsequent patent infringement suit, until the earliest of 30 months, settlement of the lawsuit and a decision in the infringement case that is favorable to the Section 505(b)(2) sponsor.

Pediatric Exclusivity

Pediatric exclusivity is a type of non-patent marketing exclusivity in the U.S. and, if granted, provides for the attachment of an additional six months of regulatory exclusivity to the term of any existing regulatory patent or regulatory

exclusivity for drug products. This six-month six month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application for a similar product.

Patent Term Restoration and Extension

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

Health Care Law and Regulation

Health care providers and third-party payors play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with providers, consultants, third-party payors and customers

---

are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, patient privacy laws and regulations and other health care laws and regulations that may constrain business and/or financial arrangements.

Restrictions under applicable federal and state health care laws and regulations, include the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal health care program such as Medicare and Medicaid; the federal civil and criminal false claims

laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious or fraudulent or knowingly making, using or causing to made or used a false record or statement to avoid, decrease or conceal an obligation to pay money to the federal government; the Foreign Corrupt Practices Act, or FCPA, which prohibits companies and their intermediaries from making, or offering or promising to make, improper payments to non-U.S. officials for the purpose of obtaining or retaining business or otherwise seeking favorable treatment; and the federal transparency requirements known as the federal Physician Payments Sunshine Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the U.S. Department of Health and Human Services, HHS, information related to payments and other transfers of value made by that entity to physicians, other healthcare providers and teaching hospitals, as well as ownership and investment interests held by physicians, and their immediate family members.

Further, some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures. Additionally, some state and local laws require the registration of pharmaceutical sales representatives in the jurisdiction. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, thus complicating compliance efforts.

Pharmaceutical Insurance Coverage and Health Care Reform

In the U.S. and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated health care costs. Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Thus, even if a product candidate is approved, sales of the product will depend, in part, on the extent to which third-party payors, including government health programs in the U.S. such as Medicare and Medicaid,

commercial health insurers and managed care organizations, provide coverage and establish adequate reimbursement levels for, the product. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable marketing approvals.

Nonetheless, product candidates may not be considered medically necessary or cost effective. A decision by a third-party payor not to cover a product could reduce physician utilization once the product is approved. Additionally, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payor to payor.

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

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

In March 2010, the U.S. Congress enacted the ACA, which, among other things, includes changes to the coverage and payment for drug products under government health care programs. Other legislative changes have been proposed and adopted since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created

---

measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2031 under the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act. These Medicare sequester reductions were suspended and reduced through the end of June 2022, with the full 2% cut resuming thereafter. 2013.

The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

These laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Indeed, under current legislation, the actual reductions in Medicare payments may vary up to 4%. four percent.

Since enactment of the ACA, there have been, and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act of 2017, or the Tax Act, which was signed by President Trump on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. On December 14, 2018 June 17, 2021, a the U.S. District Supreme Court judge in dismissed an action challenging the Northern District of Texas ruled that the individual mandate portion constitutionality of the ACA is an essential and inseverable feature of the PPACA, and therefore because the mandate was repealed as part of the Tax Act, the remaining provisions of the PPACA are invalid as well. The U.S. Supreme Court heard this case on November 10, 2020 and on June 17, 2021, dismissed this action after finding that the plaintiffs do not have standing to challenge bring the constitutionality of the ACA. action. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results.

The Trump Administration also took executive actions to undermine or delay implementation of the ACA, including directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On January 28, 2021, however, President Biden revoked those orders and issued a new Executive Order which directs federal agencies to reconsider rules and other policies that limit Americans' access to health care and consider actions that will protect and strengthen that access. Under this Order, federal agencies are directed to re-examine: policies that undermine protections for people with pre-existing conditions, including complications related to COVID-19; demonstrations and waivers under Medicaid and the ACA that may reduce coverage or undermine the programs, including work requirements; policies that undermine the Health Insurance Marketplace or other markets for health insurance; policies that make it more difficult to

enroll in Medicaid and the ACA; and policies that reduce affordability of coverage or financial assistance, including for dependents.

Pharmaceutical Price Reforms

The prices of prescription pharmaceuticals have also been the subject of considerable discussion in the United States. There have been several recent U.S. congressional inquiries, as well as proposed and enacted state and federal legislation designed to, among other things, bring more transparency to pharmaceutical pricing, review the relationship between pricing and manufacturer patient programs and reduce the costs of pharmaceuticals under Medicare and Medicaid. In 2020, President Trump issued several executive orders intended to lower the costs of prescription products and certain provisions in these orders have been incorporated into regulations. These regulations include an interim final rule implementing a most favored nation model for prices that would tie Medicare Part B payments for certain physician-

administered pharmaceuticals to the lowest price paid in other economically advanced countries, effective January 1, 2021. That rule, however, has been subject to a nationwide preliminary injunction and, on December 29, 2021, CMS issued a final rule to rescind it. With issuance of this rule, CMS stated that it will explore all options to incorporate value into payments for Medicare Part B pharmaceuticals and improve beneficiaries' access to evidence-based care.

In addition, in October 2020, the HHS and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program or SIP, to import certain prescription drugs from Canada into the United States. The final rule is currently U.S. That regulation was challenged in a lawsuit by the subject Pharmaceutical Research and Manufacturers of ongoing litigation, America, or PhRMA, but at least six the case was dismissed by a federal district court in February 2023 after the court found that PhRMA did not have standing to sue the HHS. Nine states (Vermont, Colorado, (Colorado, Florida, Maine, New Hampshire, New Mexico, North Dakota, Texas, Vermont and New Hampshire) Wisconsin) have passed laws allowing for the importation of drugs from Canada with Canada. Certain of these states have submitted Section 804 Importation Program proposals and are awaiting FDA approval. On January 5, 2024, the intent of developing SIPs FDA approved Florida's plan for review and approval by Canadian drug importation.

Further, the FDA. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The final rule would also eliminate the current safe harbor for Medicare drug rebates and create new safe harbors for beneficiary point-of-sale discounts and pharmacy benefit manager or PBM, service fees. It originally was set to go into effect on January 1, 2022, but with passage of the Inflation Reduction Act of 2022, or the IRA, (as defined below) has been delayed by Congress to January 1, 2032.

On July 9, 2021, President Biden signed Executive Order 14063, which focuses on, among other things, the price of pharmaceuticals. The Order directs the Department of Health and Human Services, or HHS to create a plan within 45 days to combat "excessive pricing of prescription pharmaceuticals and enhance domestic pharmaceutical supply chains, to reduce the prices paid by the federal government for such pharmaceuticals, and to address the recurrent problem of price gouging." On September 9, 2021, HHS released its plan to reduce pharmaceutical prices. The key features of that plan are to: (a) make pharmaceutical prices more affordable

---

and equitable for all consumers and throughout the health care system by supporting pharmaceutical price negotiations with manufacturers; (b) improve and promote competition throughout the prescription pharmaceutical industry by supporting market changes that strengthen supply chains, promote biosimilars and generic drugs, and increase

transparency; and (c) foster scientific innovation to promote better healthcare and improve health by supporting public and private research and making sure that market incentives promote discovery of valuable and accessible new treatments.

More recently, on On August 16, 2022, the Inflation Reduction Act of 2022, or IRA was signed into law by President Biden. The new legislation has implications for Medicare Part D, which is a program available to individuals who are entitled to Medicare Part A or enrolled in Medicare Part B to give them the option of paying a monthly premium for outpatient prescription drug coverage. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years.

Specifically, with respect to price negotiations, Congress authorized Medicare to negotiate lower prices for certain costly single-source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high-cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Part D drugs in 2027, 15 Part B or Part D drugs in 2028, and 20 Part B or Part D drugs in 2029 and beyond. This provision applies to drug products that have been approved for at least 9 nine years and biologics that have been licensed for 13 years, but it does not apply to drugs and biologics that have been approved for a single rare disease or condition. Further, the legislation subjects patients drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated “maximum fair price” under the law or for taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation. The new law also caps Medicare out-of-pocket drug costs at an estimated $4,000 a year in 2024 and, thereafter beginning in 2025, at $2,000 a year.

On June 6, 2023, Merck filed a lawsuit against HHS and CMS asserting that, among other things, the IRA’s Drug Price Negotiation Program for Medicare constitutes an uncompensated taking in violation of the Fifth Amendment of the Constitution. Subsequently, a number of other parties, including the U.S. Chamber of Commerce, Bristol Myers Squibb Company, the PhRMA, Astellas, Novo Nordisk, Janssen Pharmaceuticals, Novartis, AstraZeneca and Boehringer Ingelheim, also filed lawsuits in various courts with similar constitutional claims against HHS and CMS. Litigation involving these and other provisions of the IRA will continue with unpredictable and uncertain results.

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. A number of states, for example, require drug manufacturers and other entities in the drug supply chain, including health carriers, pharmacy benefit managers and wholesale distributors, to disclose information about pricing of pharmaceuticals. In addition, regional health

care organizations and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

Federal and State Data Privacy and Security laws

There are multiple privacy and data security laws that may impact our business activities, in the United States and in other countries where we conduct trials or where we may do business in the future. These laws are evolving and may increase both our obligations and our regulatory risks in the future. In the healthcare industry generally, under HIPAA, HHS has issued regulations to protect the privacy and security of protected health information used or disclosed by covered entities including certain healthcare providers, health plans and healthcare clearinghouses. HIPAA also regulates standardization of data content, codes and formats used in healthcare transactions and standardization of identifiers for health plans and providers. HIPAA also imposes certain obligations on the business associates of covered entities that obtain protected health information in providing services to or on behalf of covered entities. HIPAA may apply to us in certain circumstances and may also apply to our business partners in ways that may impact our relationships with them.

Our clinical trials will be regulated by HIPAA's Common Rule, which also includes specific privacy-related provisions. In addition to federal privacy regulations, there are a number of state laws governing confidentiality and security of health information that may be applicable to our business. In addition to possible federal civil and criminal penalties for HIPAA violations, state attorneys general are authorized to file civil actions for damages or injunctions in federal courts to enforce HIPAA and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state attorneys general (along with private plaintiffs) have brought civil actions seeking injunctions and damages resulting from alleged violations of HIPAA's privacy and security rules. State attorneys general also have authority to

enforce state privacy and security laws. New laws and regulations governing privacy and security may be adopted in the future as well.

In 2018, California passed into law the California Consumer Privacy Act, or the CCPA, which took effect on January 1, 2020 and imposed many requirements on businesses that process the personal information of California residents. Many of the CCPA's requirements are similar to those found in the General Data Protection Regulation, or the GDPR, including requiring businesses to provide notice to data subjects regarding the information collected about them and how such

information is used and shared, and providing data subjects the right to request access to such personal information and, in certain cases, request the erasure of such personal information. The CCPA also affords California residents the right to opt-out of “sales” of their personal information. The CCPA contains significant penalties for companies that violate its requirements. In November 2020, California voters passed a ballot initiative for the California Privacy Rights Act, or the CPRA, which went into effect on January 1, 2023 and significantly expanded the CCPA to incorporate additional GDPR-like provisions including requiring that the use, retention, and sharing of personal information of California residents be reasonably necessary and proportionate to the purposes of collection or processing, granting additional protections for sensitive personal information, and requiring greater disclosures related to notice to residents regarding retention of information. The CPRA also created a new enforcement agency – the California Privacy Protection Agency – whose sole responsibility is to enforce the CPRA, which will further increase compliance risk. The provisions in the CPRA may apply to some of our business activities.

In addition to California, at least eleven other states have passed comprehensive privacy laws similar to the CCPA and CPRA. These laws are either in effect or will go into effect sometime before the end of 2026. Like the CCPA and CPRA, these laws create obligations related to the processing of personal information, as well as special obligations for the processing of “sensitive” data (which includes health data in some cases). Some of the provisions of these laws may apply to our business activities. There are also states that are strongly considering or have already passed comprehensive privacy laws during the 2023 legislative sessions that will go into effect in 2024 and beyond, including New Hampshire and New Jersey. Other states will be considering these laws in the future, and Congress has also been debating passing a federal privacy law. There are also states that are specifically regulating health information that may affect our business. For example, Washington state passed a health privacy law in 2023 that will regulate the collection and sharing of health information, and the law also has a private right of action, which further increases the relevant compliance risk. Connecticut and Nevada have also passed similar laws regulating consumer health data and additional states (including Vermont) are considering such legislation for 2024. These laws may impact our business activities, including our identification of research subjects, relationships with business partners and ultimately the marketing and distribution of our products.

Review and Approval of Medicinal Products in the E.U.

In order to market any product outside of the U.S., a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, a sponsor will need to obtain the necessary approvals by the comparable non-U.S. regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. Specifically, the process governing approval of medicinal products in the E.U. generally follows the same lines as in the U.S. It entails satisfactory completion of preclinical studies and adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each proposed indication. It also requires the submission to the relevant competent authorities of an MAA and granting of a marketing authorization by these authorities before the product can be marketed and sold in the E.U.

Non-clinical Studies

Non-clinical studies are performed to demonstrate the health or environmental safety of new chemical or biological substances. Non-clinical (pharmaco-toxicological) studies must be conducted in compliance with the principles of good laboratory practice, or GLP, as set forth in E.U. Directive 2004/10/EC (unless otherwise justified for certain particular medicinal products – e.g., radio-pharmaceutical precursors for radio-labeling purposes). In particular, non-clinical studies, both in vitro and in vivo, must be planned, performed, monitored, recorded, reported and archived in accordance with the GLP principles, which define a set of rules and criteria for a quality system for the organizational process and the conditions for non-clinical studies. These GLP standards reflect the Organization for Economic Co-operation and Development requirements.

Clinical Trial Approval

On January 31, 2022, the new Clinical Trials Regulation (EU) No 536/2014, or CTR, became effective in the European Union E.U. and replaced the prior Clinical Trials Directive 2001/20/EC. The new regulation aims at simplifying and streamlining the authorization, conduct and transparency of clinical trials in the European Union. E.U. Under the new coordinated procedure for the approval

---

of clinical trials, the sponsor of a clinical trial to be conducted in more than one Member State of the European Union, E.U., or EU E.U. Member State, will only be required to submit a single application for approval. The submission will be made through the Clinical Trials Information System, a new clinical trials portal overseen by the EMA and available to clinical trial sponsors, competent authorities of the EU E.U. Member States and the public.

The main characteristics of Beyond streamlining the process, the new regulation include: a streamlined application procedure via a single entry point, the “EU Portal and Database”; includes a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures for clinical trial sponsors; and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is assessed by the appointed reporting Member State, whose assessment report is submitted for review by the sponsor and all other competent authorities of all EU member states E.U. Member States in which an application for authorization of a clinical trial has been submitted, or concerned member states. which we refer to as the Member States concerned. Part II is assessed separately by each concerned member state. Member State concerned. Strict deadlines have been established for the assessment of clinical trial applications. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the concerned member state. Member State concerned. However, overall related timelines will be defined by the Clinical Trials Regulation. CTR.

The new regulation did not change the preexisting requirement that a sponsor must obtain prior approval from the competent national authority of the EU E.U. Member State in which the clinical trial is to be conducted. If the clinical trial is conducted in different EU E.U. Member States, the competent authorities in each of these EU E.U. Member States must provide their approval for the conduct of the clinical trial. Furthermore, the sponsor may only start a clinical trial at a specific study site after the applicable ethics committee has issued a favorable opinion.

The CTR foresees a three-year transition period. The extent to which ongoing and new clinical trials will be governed by the CTR varies. Clinical trials for which an application was submitted (i) prior to January 31, 2022 under the Clinical Trials Directive, or (ii) between January 31, 2022 and January 31, 2023 and for which the sponsor has opted for the application of the Clinical Trials Directive remain governed by said Directive until January 31, 2025. After this date, all clinical trials (including those which are ongoing) will become subject to the provisions of the CTR.

As in the U.S., similar requirements for posting clinical trial information are present must be posted in the E.U. (EudraCT) website: https://eudract.ema.europa.eu/ and other countries. at the E.U. Clinical Trials Register.

PRIME Designation in the E.U.

In March 2016, the EMA launched an initiative to facilitate development of product candidates in indications, often rare, for which few or no therapies currently exist. The PRIority MEdicines, or PRIME, scheme is intended to encourage drug development in areas of unmet medical need and provides accelerated assessment of products representing substantial innovation reviewed under the centralized procedure. Products from small- and medium-sized enterprises, or SMEs, may qualify for earlier entry into the PRIME scheme than larger companies. Many benefits accrue to sponsors of product candidates with PRIME designation, including but not limited to, early and proactive regulatory dialogue with the EMA, frequent discussions on clinical trial designs and other development program elements, and accelerated MAA assessment once a dossier has been submitted. Importantly, a dedicated contact and rapporteur from the Committee for Human Medicinal Products, or CHMP, or the Committee for Advanced Therapies, or CAT, is appointed early in the PRIME scheme facilitating increased understanding of the product at EMA's committee level. A kick-off meeting initiates these relationships and includes a team of multidisciplinary experts at the EMA to provide guidance on the overall development and regulatory strategies.

Marketing Authorization

To obtain a marketing authorization for a product under E.U. regulatory systems, a sponsor must submit an MAA either under a centralized procedure administered by the EMA or one of the procedures administered by competent authorities in the E.U. Member States (either a decentralized procedure, national procedure or mutual recognition procedure). A marketing authorization may be granted only to a sponsor established in the E.U. Regulation (EC) No 1901/2006 provides that prior to obtaining a marketing authorization in the EU, E.U., sponsors have to demonstrate compliance with all measures included in an EMA-approved Pediatric Investigation Plan, or PIP, covering all subsets of the pediatric population, unless the EMA has granted (i) a product-specific waiver, (ii) a class waiver or (iii) a deferral for one or more of the measures included in the PIP.

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid across the European Economic Area, or the EEA (i.e. the E.U., as well as Iceland, Liechtenstein and Norway). Pursuant to Regulation (EC) No 726/2004, the centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy medicinal products and products with a new active substance indicated for the treatment of certain diseases, including products for the treatment of cancer. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional. The centralized procedure may also be used in certain other cases at the request of the sponsor. We anticipate that the centralized procedure will be mandatory for the product candidates we are developing.

Under the centralized procedure, the CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the E.U., the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the sponsor in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. If the CHMP accepts such request, the time limit of 210 days will be reduced to 150 days but it is possible that the CHMP can revert to the standard time limit for the centralized procedure if it considers that it is no longer appropriate to conduct an accelerated assessment. At the end of this period, the CHMP provides a scientific opinion on whether or not a marketing authorization should be granted in relation to a medicinal product. Within 15 calendar days of receipt of a final opinion from the CHMP, the European Commission must prepare a draft decision concerning an application for marketing authorization. This draft decision must take the opinion and any relevant provisions of E.U. law into account. Before arriving at a final decision on an application for centralized authorization of a medicinal product the European Commission must consult the Standing Committee on Medicinal Products for Human Use, or the Standing Committee. The Standing Committee is composed of representatives of the E.U. Member States and chaired by a non-voting European Commission representative. The European Parliament also has a related “droit de regard”. The European Parliament’s role is to ensure that the European Commission has not exceeded its powers in deciding to grant or refuse to grant a marketing authorization.

The European Commission may grant a so-called “marketing authorization under exceptional circumstances”. Such authorization is intended for products for which the sponsor can demonstrate that it is unable to provide comprehensive data on efficacy and safety under normal conditions of use, because the indications for which the product in question is intended are encountered so rarely that the sponsor cannot reasonably be expected to provide comprehensive evidence, or

in the present state of scientific knowledge, comprehensive information cannot be provided, or it would be contrary to generally accepted principles of medical ethics to collect such information. Consequently, marketing authorization under exceptional circumstances may be granted subject to certain specific obligations, which may include the following:

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

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

The European Commission may also grant a so-called "conditional marketing authorization" prior to obtaining the comprehensive clinical data required for an application for a full marketing authorization. Such conditional marketing authorizations may be granted for product candidates (including medicines designated as orphan medicinal products), if (i) the risk-benefit balance of the product candidate is positive, (ii) it is likely that the sponsor will be in a position to provide the required comprehensive clinical trial data, (iii) the product fulfills an unmet medical need and (iv) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required. A conditional marketing authorization may contain specific obligations to be fulfilled by the marketing authorization holder, including obligations with respect to the completion of ongoing or new studies and the collection of pharmacovigilance data. Conditional marketing authorizations are valid for one year, and may be renewed annually, if the risk-benefit balance remains positive, and after an assessment of the need for additional or modified conditions and/or specific obligations. The timelines for the centralized procedure described above also apply with respect to the review by the CHMP of applications for a conditional marketing authorization.

Unlike the centralized authorization procedure, the decentralized marketing authorization procedure requires a separate application to, and leads to separate approval by, the competent authorities of each E.U. Member State in which the product is to be marketed. This application is identical to the application that would be submitted to the EMA for authorization through the centralized procedure. The reference E.U. Member State prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. The resulting assessment report is submitted to the concerned E.U. Member States who, within 90 days of receipt, must decide whether to approve the assessment report

and related materials. If a concerned E.U. Member State cannot approve the assessment report and related materials due to

concerns relating to a potential serious risk to public health, disputed elements may be referred to the European Commission, whose decision is binding on all E.U. Member States.

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

Regulatory Data Protection in the E.U.

In the E.U., innovative medicinal products approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Directive 2001/83/EC. Regulation (EC) No 726/2004 repeats this entitlement for medicinal products authorized in accordance the centralized authorization procedure. Data exclusivity prevents sponsors for authorization of generics of these innovative products from referencing the innovator's data to assess a generic (abridged) application for a period of eight years. During an additional two-year period of market exclusivity, a generic MAA can be submitted and authorized, and the innovator's data may be referenced, but no generic medicinal product can be placed on the E.U. market until the expiration of the market exclusivity. The overall 10-year period will be extended to a maximum of 11 years if, during the first eight years of those 10 years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be an NCE so that the innovator gains the prescribed period of data exclusivity, another company nevertheless could also market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Patent Term Extensions in the E.U. and Other Jurisdictions

The E.U. also provides for patent term extension through Supplementary Protection Certificates, or SPCs. The rules and requirements for obtaining a SPC are similar to those in the U.S. An SPC may extend the term of a patent for up to five years after its originally scheduled expiration date and can provide up to a maximum of fifteen years of marketing

exclusivity for a drug. These periods can be extended for six additional months if pediatric exclusivity is obtained, which is described in detail below. Although SPCs are available throughout the E.U., sponsors must apply on a country-by-country basis. Similar patent term extension rights exist in certain other foreign jurisdictions outside the E.U.

Periods of Authorization and Renewals

A marketing authorization has an initial validity for five years in principle. The marketing authorization may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the EMA or by the competent authority of the E.U. Member State. To this end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. The European Commission or the competent authorities of the E.U. Member States may decide, on justified grounds relating to pharmacovigilance, to proceed with one further five-year period of marketing authorization. Once subsequently definitively renewed, the marketing authorization shall be valid for an unlimited period. Any authorization which is not followed by the actual placing of the medicinal product on the E.U. market (in case of centralized procedure) or on the market of the authorizing E.U. Member State within three years after authorization ceases to be valid (the so-called sunset clause).

Pediatric Studies and Exclusivity

Prior to obtaining a marketing authorization in the E.U., sponsors must demonstrate compliance with all measures included in an EMA-approved PIP covering all subsets of the pediatric population, unless the EMA has granted a product-specific waiver, a class waiver, or a deferral for one or more of the measures included in the PIP. The respective requirements for all marketing authorization procedures are laid down in Regulation (EC) No 1901/2006, the so-called Pediatric Regulation. This requirement also applies when a company wants to add a new indication, pharmaceutical form or route of administration for a medicine that is already authorized. The Pediatric Committee of the EMA, or PDCO, may grant deferrals for some medicines, allowing a company to delay development of the medicine for children until there is enough information to demonstrate its effectiveness and safety in adults. The PDCO may also grant waivers when development of a medicine for children is not needed or is not appropriate, such as for diseases that only affect the elderly population. Before an MAA can be filed, or an existing marketing authorization can be amended, the EMA must determine that a company actually complied with the agreed studies and measures listed in each relevant PIP. If a sponsor obtains a marketing authorization in all E.U. Member States, or a marketing authorization granted in the Centralized Procedure by the European Commission, and the study results for the pediatric population are included in the product information, even when negative, the medicine is then eligible for an additional six-month period of qualifying patent protection through extension of the term of the Supplementary Protection Certificate.

Regulatory Requirements after a Marketing Authorization has been Obtained

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

- Compliance with the E.U.'s stringent pharmacovigilance or safety reporting rules must be ensured. These rules can impose post-authorization studies and additional monitoring obligations.
- The manufacturing of authorized medicinal products, for which a separate manufacturer's license is mandatory, mus also be conducted in strict compliance with the applicable E.U. laws, regulations and guidance, including Directive 2001/83/EC, Directive 2003/94/EC, Regulation (EC) No 726/2004 and the European Commission Guidelines for Go Manufacturing Practice, or E.U. cGMP. These requirements include compliance with E.U. cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients, including the manufacture of active pharmaceutical ingredients outside of the E.U. with the intention to import the active pharmaceutical ingredients into the E.U.
- The marketing and promotion of authorized drugs, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs and/or the general public, are strictly regulated in the E.U. notal under Directive 2001/83EC, as amended, and E.U. Member State laws. Direct-to-consumer advertising of prescripti medicines is prohibited across the E.U.

Brexit and the Regulatory Framework in the U.K.

The United Kingdom's U.K.s withdrawal from the EU E.U., which is sometimes referred to as Brexit, took place on January 31, 2020. The EU E.U. and the U.K. reached an agreement on their new partnership in the Trade and Cooperation Agreement, or the Agreement, which was applied provisionally beginning on January 1, 2021 , and which entered into force on May 1, 2021. The Agreement focuses This agreement focused primarily on free trade by ensuring no tariffs or quotas on trade in goods, including healthcare products such as medicinal products. Thereafter, the EU The E.U. and the U.K. will form formed two separate markets governed by two distinct regulatory and legal regimes. As such, the Agreement seeks regimes, except that Northern Ireland continued to minimize barriers to trade in goods while accepting that border checks will become inevitable broadly follow E.U. laws as a consequence that the U.K. is no longer part of the single market. further described below. As of January 1, 2021, the MHRA became responsible for supervising medicines and medical devices in Great Britain, comprising England, Scotland and Wales under domestic law whereas Northern Ireland continues continued to be subject to EU E.U. rules under the Northern Ireland Protocol. The

On February 27, 2023, the U.K. government and the European Commission announced a political agreement in principle to replace the Northern Ireland Protocol with a new set of arrangements, known as the "Windsor Framework". This new framework fundamentally changes the existing system under the Northern Ireland Protocol, including with respect to the regulation of medicinal products in the U.K. In particular, the MHRA will rely be responsible for approving all medicinal products destined for the U.K. market (i.e., Great Britain GB and Northern Ireland), and the EMA will no longer have any

role in approving medicinal products destined for Northern Ireland. A single U.K.-wide marketing authorization, or MA, will be granted by the MHRA for all medicinal products to be sold in the U.K., enabling products to be sold in a single pack and under a single authorization throughout the U.K. The Windsor Framework was approved by the E.U.-U.K. Joint Committee on March 24, 2023, so the U.K. government and the E.U. will enact legislative measures to bring it into law. On June 9, 2023, the MHRA announced that the medicines aspects of the Windsor Framework will apply from January 1, 2025. The Human Medicines Regulations 2012 (SI 2012/1916) (as amended), or (or the HMR, as HMR), is the basis primary legal instrument for regulating medicines. the regulation of medicines in the U.K. The HMR has incorporated into the domestic law the body of EU E.U. law instruments governing medicinal products that pre-existed prior to the U.K.'s withdrawal from the EU. The MHRA E.U.

E.U. laws which have been transposed into U.K. law through secondary legislation continue to be applicable as "retained E.U. law". However, new legislation such as the CTR will not be applicable in Great Britain. Since a significant proportion of the regulatory framework for pharmaceutical products in the U.K. covering the quality, safety, and efficacy of pharmaceutical products, clinical trials, MAs, commercial sales, and distribution of pharmaceutical products is derived from E.U. directives and regulations, Brexit may rely on have a decision taken material impact upon the regulatory regime with respect to the development, manufacture, importation, approval, and commercialization of our product candidates in the U.K. For example, the U.K. is no longer covered by the European Commission centralized procedures for obtaining E.U.-wide MAs from the EMA, and a separate MA will be required to market our product candidates in the U.K. A new international recognition framework has been in place since January 1, 2024, whereby the MHRA will have regard to decisions on the approval of MAs made by the EMA and certain other regulators when determining an application for a new marketing authorization via the centralized procedure until December 31, 2023. Great Britain MA.

Furthermore, while the Data Protection Act of 2018 in the U.K. that "implements" and complements the EU General Data Protection Regulation, or the GDPR, is now effective in the U.K., it is still unclear whether transfer of data from the EEA to the U.K. will remain lawful under the GDPR. The Trade and Cooperation Agreement provides for a transitional period during which the U.K. will be treated like an EU Member State in relation to processing and transfers of personal data for four months from January 1, 2021. This may be extended by two further months. After such period, the U.K. will be a "third country" under the GDPR unless the European Commission adopts an adequacy decision in respect of transfers of personal data to the U.K. The U.K. has already determined that it considers all of the E.U. and EEA member states to be adequate for the purposes of data protection, ensuring that data flows from the U.K. to the E.U. and EEA remain unaffected. We may, however, incur liabilities, expenses, costs, and other operational losses under the GDPR and applicable EU Member States and the U.K. privacy laws in connection with any measures we take to comply with them.

General Data Protection Regulation

The collection, use, disclosure, transfer or other processing of personal data regarding individuals in the EU, E.U., including personal health data, is subject to the GDPR. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals

regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the EU, E.U., including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% four percent of annual global revenues, whichever is greater. The GDPR also confers a private right of action on

---

data subjects patients and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR is a rigorous and time-intensive process that may increase the cost of doing business or require companies to change their business practices to ensure full compliance. In July 2020, the Court of Justice of the European Union, or the CJEU, invalidated the EU-U.S. E.U.-U.S. Privacy Shield framework, one of the mechanisms used to legitimize the transfer of personal data from the EEA to the United States. The CJEU decision also drew into question the long-term viability of an alternative means of data transfer, the standard contractual clauses, for transfers of personal data from the EEA to the United States. U.S.

Additionally, Following the CJEU decision, in October 2022, President Biden signed an executive order to implement the EU-U.S. E.U.-U.S. Data Privacy Framework, which would serve as a replacement to the EU-US E.U.-U.S. Privacy Shield. The European Commission initiated the process to adopt an adequacy decision for the EU-US E.U.-U.S. Data Privacy Framework in December 2022. It is unclear if 2022, and when has now adopted an adequacy decision to permit data transfers from the framework will be finalized E.U. to the U.S. going forward. This development permits data transfers under the E.U.-U.S. Data Privacy Framework and whether it will be more broadly has made international data transfers more straightforward, but these provisions are being challenged in court. The continuing uncertainty around this issue may further impact our business operations in the EU. E.U. We may, however, incur liabilities, expenses, costs, and other operational losses under the GDPR and the laws of applicable E.U. Member States and the U.K. privacy laws in connection with any measures we take to comply with them.

Beyond the GDPR, there are privacy and data security laws in a growing number of countries around the world. While many loosely follow the GDPR as a model, other laws contain different or conflicting provisions. These laws may impact our ability to conduct our business activities, including both our clinical trials and any eventual sale and distribution of commercial products.

Pricing Decisions for Approved Products

In the E.U., pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies or so-called health technology assessments, in order to obtain reimbursement or pricing approval. For example, the E.U. provides options for the E.U. Member States to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. E.U. Member States may approve a specific price for a product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other E.U. Member States allow companies to fix their own prices for products, but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the E.U. have increased the amount of discounts required on pharmaceuticals and these efforts could continue as countries attempt to manage health care expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the E.U. The downward pressure on health care costs in general, particularly with respect to prescription products, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various E.U. Member States, and parallel trade, i.e., arbitrage between low-priced and high-priced E.U. Member States, can further reduce prices. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any products, if approved in those countries.

Employees and Human Capital Resources

As of December 31, 2022 December 31, 2023, we had 25 employees, with 16 15 employees engaged in research and development and the remaining nine 10 engaged in general management and administration, including finance and commercial. None of our employees are represented by labor unions or covered by collective bargaining agreements. We believe that we maintain good relations with our employees.

Our human capital resources objectives include, as applicable, identifying, recruiting, retaining, incentivizing and integrating our existing and additional employees. The principal purposes of our equity incentive plans are to attract, retain and motivate selected employees, consultants and directors through the granting of stock-based compensation awards in ways that are aligned with the interests of our stockholders. We value our employees and regularly benchmark total rewards we provide, such as short- and long-term compensation, 401(k) contributions, health, welfare and quality of life benefits, paid time off and personal leave, against our industry peers to ensure we remain competitive and attractive to potential new hires.

Our Corporate Information

We were incorporated under the laws of the State of Delaware on March 17, 2011 under the name Trevi Therapeutics, Inc. Our principal executive offices are located at 195 Church Street, 16th Floor, New Haven, Connecticut 06510, and our telephone number is (203) 304-2499. Our website address is www.trevitherapeutics.com. The information

contained on, or that can be accessed through, our website is not a part of this Annual Report on Form 10-K. We have included our website address in this Annual Report on Form 10-K solely as an inactive textual reference.

Item 1A. Risk Factors.

Our business is subject to numerous risks. The following important factors, among others, could cause our actual results to differ materially from those expressed in forward-looking statements made by us or on our behalf in this Annual Report on Form 10-K and other filings with the Securities and Exchange Commission, press releases, communications with investors, and oral statements. Actual future results may differ materially from those anticipated in our forward-looking statements. We undertake no obligation to update any forward-looking statements, whether as a result of new information, future events, or otherwise.

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred significant losses since inception, expect to incur significant and increasing losses for the foreseeable future and may never achieve or maintain profitability.

We have incurred significant annual net losses every year since our inception. We expect to continue to incur significant and increasing net losses for at least the next several years. Our net losses were $29.2 million $29.1 million and $33.9 million $29.2 million for the years ended December 31, 2022 December 31, 2023 and 2021, 2022, respectively. As of December 31, 2022 December 31, 2023, we had an accumulated deficit of $210.1 million $239.1 million. We have not generated any revenues from product sales, have not completed the development of any product candidate and may never have a product candidate approved for commercialization. We have financed our operations to date primarily through private placements of our convertible preferred stock and convertible notes prior to our initial public offering, or IPO, borrowings under our prior term loan facility, proceeds from our IPO, and concurrent private placement completed in May 2019, sales of our common stock pursuant and warrants to an ATM Sales Agreement, the term loan facility with Silicon Valley Bank that we entered into in August 2020, which we refer to as the SVB Term Loan, proceeds from the two private placements we completed in October 2021, or the October 2021 Private Placements, proceeds from the private placement we completed in April 2022, or the April 2022 Private Placement, proceeds from the exercise of purchase our common stock, warrants that were issued in the October 2021 Private Placements and proceeds borrowings from the public offering we completed in September 2022, or the September 2022 Offering. term loans. We have devoted substantially all our financial resources and efforts to the clinical development of our product candidate Haduvio and related activities. Our net losses may fluctuate significantly from quarter to quarter and year to year. Net losses and negative cash flows have had, and will continue to have, an adverse effect on our stockholders' equity and working capital.

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

- continue to develop and conduct clinical trials of Haduvio, including the next trials we plan to conduct for our Phase 2b CORAL clinical trial of Haduvio for the treatment of chronic cough in adults with idiopathic pulmonary fibrosis, or IPF, our planned Phase 2 2a RIVER clinical trial of Haduvio for the treatment of refractory chronic cough, or RCC, and the secon part of our human abuse potential, or HAP, study, and our ongoing human abuse liability, or HAL, study; planned Phase clinical trial to evaluate the effect of Haduvio on respiratory physiology in patients with IPF of varying disease severity;
- complete other development work required for the filing of a new drug application, or NDA, with the U.S. Food and Drug Administration, or FDA, and the filing of marketing authorization applications, or MAAs, with the European Medicines Agency, or EMA and the Medicines and Healthcare Products Regulatory Agency in the United Kingdom, or MHRA, or ot government agencies, for Haduvio;
- seek regulatory and marketing approvals for Haduvio for the treatment of chronic cough in adults with IPF, other chronic cough indications, or RCC and/or for the treatment of prurigo nodularis or for any future product candidate that successf completes clinical trials, if any;
- negotiate and execute pediatric development plans and complete any post-approval commitments;
- establish sales, marketing, distribution and other commercial infrastructure to commercialize any products for which we may obtain marketing approval;
- require the manufacture of larger quantities of Haduvio or any future product candidate for clinical development and, potentially, commercialization;
- acquire or in-license rights to other potential product candidates or technologies;
- initiate and conduct research, preclinical and clinical development efforts for any future product candidates;
- maintain, expand and protect our intellectual property portfolio;
- hire and retain additional personnel, such as clinical, regulatory and scientific personnel;

- add operational, financial and management information systems and personnel, including personnel to support our prod development and commercialization efforts and to help us comply with our obligations as a public company; and
- add equipment and physical infrastructure to support our development program for Haduvio and for any future product candidates.

Our ability to become and remain profitable depends on our ability to generate revenue. We do not expect to generate significant revenue unless and until we are able to obtain marketing approval for and successfully commercialize Haduvio or any future product candidate. Successful commercialization will require achievement of key milestones, including completing clinical trials of Haduvio or any future product candidate, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those products for which we may obtain marketing approval, satisfying any post-marketing requirements and obtaining reimbursement for any such product from private insurance or government payors. For example, in order to successfully commercialize Haduvio for the treatment of prurigo nodularis, chronic cough in IPF, we are may be required, at a minimum, to successfully complete an two additional Phase 3 clinical trial trials prior to submitting an NDA and MAA to regulatory authorities to obtain marketing approval. Because of the uncertainties and risks associated with these activities, we are unable to accurately predict the timing and amount of revenues and if or when we might achieve profitability. We may never succeed in these activities and, even if we do, we may never generate revenues that are large enough for us to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, expand our business, maintain our development efforts, develop a pipeline of product candidates or continue our operations.

We have a limited operating history and no products approved for commercial sale, which may make it difficult to evaluate the prospects for our future success and viability.

We were founded and commenced operations in 2011. Our operations to date have been limited to financing and staffing our company and conducting preclinical and clinical development of Haduvio. We have not yet demonstrated an ability to successfully complete clinical development of any product candidates, obtain marketing approvals, manufacture a commercial-scale product or arrange for a third-party to do so on our behalf or conduct sales and marketing activities necessary for successful commercialization of any products. Accordingly, you should consider our prospects in light of the costs, uncertainties, delays and difficulties frequently encountered by clinical-stage biopharmaceutical companies such as ours. Any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history or a history of successfully developing and commercializing pharmaceutical products.

We may encounter unforeseen expenses, difficulties, complications, delays and other known or unknown factors in achieving our business objectives. If we obtain marketing approval for Haduvio or any future product candidate, we will need to transition from a company focused on clinical development to a company capable of supporting commercial activities. We may not be successful in effectuating such a transition.

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

We will need substantial additional funding and if we are unable to raise sufficient capital when needed on acceptable terms or at all, we could be forced to delay, reduce or abandon our product development programs or commercialization efforts.

Developing pharmaceutical products, including conducting preclinical and nonclinical studies and clinical trials, is a very time-consuming, expensive and uncertain process that takes years to complete. We have consumed substantial amounts of cash since our inception. For example, in the years ended December 31, 2022 December 31, 2023 and 2021, 2022, we used net cash of $28.2 million $31.7 million and $28.9 million $28.2 million, respectively, in our operating activities, substantially all of which related to development activities for Haduvio. As of December 31, 2022 December 31, 2023, our cash, cash equivalents and marketable securities were $120.5 million $83.0 million. We expect our expenses to increase substantially in connection with our ongoing activities, particularly as we continue to develop Haduvio, including as we:

- conduct the next trials we plan to conduct for our Phase 2b CORAL clinical trial of Haduvio for the treatment of chronic cough in adults with IPF;
- conduct our planned Phase 2 1b clinical trial to evaluate the effect of Haduvio on respiratory physiology in patients with I of varying disease severity;
- conduct our Phase 2a RIVER clinical trial of Haduvio for the treatment of refractory chronic cough; RCC; and
- complete conduct the second part of our HAL HAP study to further characterize compare the abuse potential of oral nalbuphine ER. to intravenous, or IV, butorphanol.

In addition, we may incur additional expenses:

- if we determine to conduct an additional clinical trial of Haduvio for the treatment of prurigo nodularis; and

---

- if we acquire or in-license rights to other potential product candidates or technologies and seek regulatory and marketin approvals for Haduvio or any future product candidate that successfully completes clinical trials; and
- as a result of the COVID-19 pandemic or other outbreaks of infectious disease and resulting clinical trial delays and interruptions. trials.

In addition, if we obtain marketing approval for Haduvio or any future product candidate, we may incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. For instance, we currently intend to commercialize Haduvio in the U.S. ourselves by developing a focused, specialty sales, marketing and distribution organization. Furthermore, we expect to continue to incur significant costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are

unable to raise sufficient capital when needed on acceptable terms or at all, we may be forced to delay, reduce or abandon our development programs or any future commercialization efforts.

We plan to use our existing cash, cash equivalents and marketable securities to fund the development of Haduvio and for working capital and other general corporate purposes. We will be required to expend significant funds to advance the development of Haduvio in multiple indications, as well as any future product candidates we may seek to develop. Our existing cash, cash equivalents and marketable securities will not be sufficient to complete development of Haduvio for the treatment of chronic cough in adults with IPF, for refractory chronic cough RCC or for prurigo nodularis, or for any other condition or of any future product candidate. We do not have any committed external source of funds. Accordingly, we will be required to obtain further funding through public or private equity offerings, debt financings, collaborations and licensing arrangements or other sources to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms or at all. Our failure to raise capital as and when needed would have a negative impact on our financial condition and our ability to pursue our business strategy.

We believe that our existing cash, cash equivalents and marketable securities will enable us to fund our operating expenses and capital expenditure requirements into 2026. Our current plans do not take into account the cost of any additional clinical trials for the treatment of prurigo nodularis.

We have based our estimates as to how long we expect we will be able to fund our operations on assumptions that may prove to be wrong and we could use our available capital resources sooner than we currently expect, in which case we would be required to obtain additional financing. However, such a financing may not be available to us on acceptable terms, on a timely basis or at all. In addition, under the terms of the Securities Purchase Agreements we entered into with our October 2021 Private Placements, until April 5, 2023, we are prohibited from obtaining additional financing through a variable rate transaction such as an equity line of credit. Our failure to raise capital as and when needed would have a negative impact on our financial condition and our ability to pursue our business strategy.

Further, changing circumstances, some of which may be beyond our control, could cause us to consume capital significantly faster than we currently anticipate and we may need to seek additional funds sooner than planned. Our future funding requirements, both short-term and long-term, will depend on many factors including:

- the scope, progress, timing, costs and results of clinical trials of Haduvio, including the next our Phase 2b CORAL clinica trials trial of Haduvio for the treatment of chronic cough in adults with IPF, our Phase 2a RIVER clinical trial in RCC, the second part of our HAP study, and our planned Phase 2 1b clinical trial to evaluate the effect of Haduvio on respiratory physiology in refractory chronic cough, and our ongoing HAL study, patients with IPF of varying disease severity, as well trials for any future product candidates;
- the number and characteristics of indications for which we seek to develop Haduvio or any future product candidates an their respective development requirements;
- the outcome, timing and costs of clinical and nonclinical trials and of seeking regulatory approvals, including the costs o supportive clinical studies such as our ongoing HAL study and a potential Thorough QT, or TQT, study;
- the costs associated with the manufacture of necessary quantities of Haduvio or any future product candidate for clinica development in connection with regulatory submissions;
- the costs of commercialization activities for Haduvio for the treatment of chronic cough in adults with IPF or any other

chronic cough indications and RCC or for any future product candidates that receive marketing approval, if any, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities;

- subject to receipt of marketing approvals, revenue, if any, received from commercial sales of Haduvio for the treatment of chronic cough in adults with IPF or for any other chronic cough indications RCC or for the treatment of prurigo nodularis, from any future product candidates;
- our ability to identify potential collaborators for Haduvio for the treatment of prurigo nodularis or for the treatment of chronic cough in adults with IPF or for any other chronic cough indications RCC or for any future product candidates, and the terms and timing of any collaboration agreement that we may establish for the development and any commercialization of such product candidates;
- the extent to which we acquire or in-license rights to other potential product candidates or technologies and the terms and timing of any such acquisition or licensing arrangements;

- our potential obligation to make milestone payments to Endo, which would become due upon the successful completion of the first Phase 3 clinical trial of a licensed product candidate and the marketing approval of a licensed product in the United States, as well as our potential obligations to pay Endo royalties on the net sales of the product;
- our headcount growth and associated costs as we expand our research and development activities and medical affairs activities and establish a commercial infrastructure;
- the costs of preparing, filing and prosecuting patent applications, maintaining, expanding and protecting our intellectual property rights and defending against intellectual property-related claims;
- the effect of competing technologies and market developments;
- our ability to establish and maintain healthcare coverage and adequate reimbursement for our products; and
- the costs of operating as a public company; and company.
  - the impact of the COVID-19 pandemic and other outbreaks of infectious disease on the scope, progress, timing, costs and results of our ongoing and planned clinical trials of Haduvio.

Our indebtedness could adversely affect our financial condition or restrict our future operations.

On August 13, 2020, we entered into a Loan and Security Agreement, or the SVB Loan Agreement with Silicon Valley Bank, or SVB, pursuant to which SVB provided a term loan to us in the original principal amount of $14.0 million, or the SVB Term Loan. The SVB Term Loan bears interest at a floating rate per annum equal to the greater of (A) the prime rate plus 3.00% and (B) 6.25%. The Federal Reserve has recently raised interest rates to combat the effects of recent high

inflation and may raise interest rates further in the future. The increase in interest rates by the Federal Reserve has caused, and could in the future continue to cause, the prime rate to increase, which has increased and could in the future further increase our debt service obligations. Significant increases in such obligations could have a negative impact on our financial position or operating results, including cash available for servicing our indebtedness.

On the first business day of each month, we are required to make monthly interest payments and commencing on March 1, 2022, we were required to repay the SVB Term Loan in 24 consecutive installments of principal plus monthly payments of accrued interest. All outstanding principal and accrued and unpaid interest under the SVB Term Loan and all other outstanding obligations with respect to the SVB Term Loan are due and payable in full on February 1, 2024. Our obligations under the Loan Agreement are secured by substantially all of our assets, excluding our intellectual property (which is subject to a negative pledge under the Loan Agreement). The SVB Loan Agreement also includes customary affirmative and negative covenants, including a requirement to maintain our bank accounts with SVB or bank accounts that are subject to SVB's control and limitations on transferring all or any part of our business or property, changing our business, liquidating or dissolving, permitting a change in control, adding new offices or business locations, changing jurisdiction of organization, organizational structure or legal name, merging with or acquiring another entity, incurring additional indebtedness, creating any lien on our property, paying dividends or redeeming stock, entering into material transactions with an affiliate or making payments on subordinated debt. On March 10, 2023, the Federal Deposit Insurance Corporation ("FDIC") issued a press release stating that Silicon Valley Bank, Santa Clara, California, ("SVB") was closed by the California Department of Financial Protection and Innovation, which appointed the FDIC as receiver. Since March 13, 2023, SVB has operated as Silicon Valley Bridge Bank under the FDIC receivership. In light of the status of SVB and operational difficulties we have had in using SVB's cash management platform, we have considered and may consider in the future moving our bank accounts and cash resources to other financial institutions, which action could result in SVB declaring us to be in default under the Term Loan. The remaining principal balance of the SVB Term Loan at December 31, 2022 was $8.2 million and at March 16, 2023 was $6.4 million.

Our debt combined with our other financial obligations and contractual commitments could have significant adverse consequences, including:

- requiring us to dedicate a portion of our cash and cash equivalents to the payment of interest on and principal of ou debt, which will reduce the amounts available to fund working capital, capital expenditures, product development efforts and other general corporate purposes;
- exposing us to the risk of interest rate volatility as the SVB Term Loan is subject to a floating interest rate;
- obligating us to negative covenants restricting our activities, including the negative covenants to which we are subje under the SVB Loan Agreement; and
- limiting our flexibility in planning for or reacting to, changes in our business and our industry.

We intend to satisfy our debt service obligations with our existing cash, cash equivalents and marketable securities, proceeds from the exercise of any warrants from the October 2021 Private Placements, and any additional amounts we may raise through future debt and equity financings. However, we may not have sufficient funds or may be unable to

arrange for additional financing to pay the amounts due under our existing debt. Funds from external sources may not be available on acceptable terms, if at all. Failure to pay any amount due under the SVB Loan Agreement, to comply with covenants under the SVB Loan Agreement or the occurrence of an event that would reasonably be expected to have a material adverse effect on our business, operations or condition (financial or otherwise) would result in an event of default. The occurrence and continuation of an event of default, including if we were to move our bank accounts and cash resources, could cause interest to be charged at the rate that is otherwise applicable plus 5.00% (unless SVB elects to impose a smaller increase) and would provide SVB with the right to accelerate all obligations under the SVB Loan Agreement and exercise remedies against us and the collateral securing the SVB Term Loan and other obligations under the SVB Loan Agreement, including foreclosure against assets securing the SVB Term Loan and other obligations under the SVB Loan Agreement, including our cash. In addition, the covenants under the SVB Loan Agreement and the pledge of substantially all our assets, excluding our intellectual property (which is subject to a negative pledge under the SVB Loan Agreement), as collateral on the SVB Term Loan may limit our ability to obtain additional debt financing.

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

We expect our expenses to increase substantially in connection with our planned operations, particularly as we:

- conduct the next our Phase 2b CORAL clinical trials we plan to conduct for trial of Haduvio for the treatment of chronic cough in adults with IPF;
- conduct our planned Phase 2 1b clinical trial to evaluate the effect of Haduvio on respiratory physiology in patients with I of varying disease severity;
- conduct our Phase 2a RIVER clinical trial of Haduvio for the treatment of refractory chronic cough; RCC; and
- complete conduct the second part of our HAL HAP study to further characterize the abusive abuse potential of oral nalbuphine ER. nalbuphine.

Accordingly, we will be required to obtain further funding through public or private equity offerings, debt financings, collaborations and licensing arrangements or other sources to fund these expenses. To the extent that we raise additional capital through the sale of common stock, convertible securities or other equity securities, your ownership interest may be diluted, and the terms of these securities could include liquidation or other preferences and anti-dilution protections that could adversely affect your rights as a common stockholder.

Our ability to obtain further debt financing may be limited by the covenants under the SVB Loan Agreement, which include a covenant not to incur additional indebtedness as well as the pledge of substantially all our assets, excluding our intellectual property (which is subject to a negative pledge under the SVB Loan Agreement), as collateral on the SVB Term Loan. In addition, further debt Debt financing, if available, would result in additional fixed payment obligations and may involve agreements that include grants of additional security interests on our assets and additional restrictive covenants that limit our ability to take specific actions, such as incurring additional debt, making capital expenditures, granting liens over our assets, redeeming stock or declaring dividends, that could adversely impact our ability to conduct our business, which covenants may be more restrictive than the covenants to which we are subject under the SVB Loan Agreement. business.

Securing financing could also require a substantial amount of time from our management and may divert a disproportionate amount of their attention away from daily activities, which may adversely affect our management's ability to oversee the development of Haduvio or that of any future product candidates. If we raise additional funds through collaborations or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to future revenue streams or product candidates or grant licenses on terms that may not be favorable to us.

Risks Related to the Development and Commercialization of Haduvio and Any Future Product Candidates

We are dependent on the successful development and commercialization of Haduvio, our sole product candidate. If we are unable to complete the clinical development of, obtain marketing approval for or successfully commercialize Haduvio or if we experience significant delays in doing so, our business would be substantially harmed.

We currently have no products approved for sale and are investing substantially all our efforts and financial resources to fund the development and commercialization of Haduvio for the treatment of chronic cough in adults with IPF and other chronic cough indications, and for the treatment of prurigo nodularis. RCC. Our prospects are dependent on our ability to develop, obtain marketing approval for and successfully commercialize Haduvio in one or more indications as we currently have no other product candidates under development. We may acquire or in-license rights to other potential product candidates or technologies in the future, but we are currently not developing any other product candidates.

Our most advanced programs are the development of Haduvio for the treatment of chronic cough in adults with IPF and for the treatment of prurigo nodularis. RCC. As a result, if our efforts to develop and commercialize Haduvio for the treatment of chronic cough in adults with IPF or other chronic cough indications or for the treatment of prurigo nodularis RCC are unsuccessful or we experience significant delays in doing so, our business could also be substantially harmed.

The success of Haduvio for the treatment of chronic cough in adults with IPF and other chronic cough conditions and for the treatment of prurigo nodularis RCC will depend on several factors, including the following:

- initiating and successfully recruiting, enrolling and retaining subjects patients in and completing additional clinical and nonclinical trials of Haduvio, including the additional clinical trials we are conducting and plan to conduct for the treatme of chronic cough in adults with IPF, one of which are is subject to the submission and clearance by the FDA of an IND; II and RCC;

- completing the analysis of the open-label extension portion second part of our Phase 2b/3 PRISM trial and determining t next steps for the program after discussions with the FDA; HAP study;
- completing other supportive clinical studies such as our ongoing HAL study, a potential studies of physical dependence study and a potential Thorough QT study; TQT;
- demonstrating safety, tolerability and efficacy profiles that are satisfactory to the FDA, EMA, MHRA and other comparab regulatory authorities for marketing approval;
- receiving timely marketing approvals from applicable regulatory authorities;
- managing the extent and cost of any required post-marketing approval commitments to applicable regulatory authorities
- establishing and maintaining arrangements with our third-party supplier of drug substance for Haduvio;
- establishing and maintaining arrangements with third-party manufacturers of Haduvio, including developing, validating a maintaining a commercially viable manufacturing process that is compliant with current good manufacturing practices, o cGMPs;
- obtaining, maintaining and protecting our patents, trade secrets and regulatory exclusivity in the U.S. and other countrie
- establishing a focused, specialty sales organization in the U.S. and successfully launching commercial sales following a marketing approval;
- obtaining commercial acceptance of our products, if approved, by patients, the medical community and third-party payo and obtaining and maintaining healthcare coverage and adequate reimbursement;
- maintaining an acceptable safety profile following any marketing approval; and
- our ability to compete with other therapies.

Many of these factors are beyond our control, including the clinical development and regulatory approval process; potential threats to our intellectual property rights; and the manufacturing, marketing and sales efforts, respectively, of any current or future third-party contractors. If we are unable to develop, receive marketing approval for and successfully commercialize Haduvio or if we experience delays as a result of any of these factors or otherwise, our business would be substantially harmed.

Our approach to the development and commercialization of Haduvio to treat chronic cough is unproven.

We are currently focused on the development and commercialization of Haduvio for the treatment of chronic cough in adults with IPF and other chronic cough indications. RCC. Haduvio is an oral extended-release formulation of nalbuphine, the active drug ingredient in Haduvio, which is a mixed κ-opioid receptor agonist and μ-opioid receptor antagonist that has been approved and marketed as an injectable for pain indications for more than 20 years in the U.S. and Europe. Nalbuphine is currently not commercially available in an oral dosage form, such as Haduvio. While we believe that nalbuphine's dual mechanism of action, which targets both the central and peripheral nervous systems, makes Haduvio a promising potential therapy for the treatment of chronic cough and that Haduvio has the potential to be safe and well-tolerated, nalbuphine has not been approved in any indications other than pain. pain and balanced anesthesia. Additionally, Haduvio has not been approved in any indication. No therapies have been approved in the U.S. or Europe for the treatment of chronic cough in adults with IPF and we no therapies have been approved in the U.S. or outside the U.S. (with the

exception of Japan and Switzerland) for the treatment of RCC. We can provide no assurance that either Haduvio or any other future product candidate that we may seek to develop for this indication chronic cough indications will be effective or safe, obtain regulatory approval or be commercially successful.

Clinical drug development involves a lengthy and expensive process with an uncertain outcome.

We are not permitted to commercialize, market, promote or sell any product candidate in the U.S. without obtaining marketing approval from the FDA. Foreign regulatory authorities, such as the EMA and MHRA, impose similar requirements. We must complete extensive clinical trials to demonstrate the safety and efficacy of Haduvio and any future product candidate in humans and complete required regulatory submissions before we will be able to obtain these approvals. We may never receive such approvals.

Clinical testing is expensive, is difficult to design and implement, can take many years to complete and is inherently uncertain as to outcome. The clinical development of Haduvio and any future product candidate is susceptible to the risk of

---

failure at any stage of product development and we may experience numerous unforeseen events during or as a result of, clinical trials that could delay or prevent clinical development, marketing approval or commercialization of Haduvio or any future product candidate, including:

- clinical trials may produce unfavorable or inconclusive results;
- we may decide, or regulators may require us, to restructure clinical trials, conduct additional clinical and nonclinical trials abandon product development programs;
- we may experience delays in obtaining authorization to commence a clinical trial from regulators, clinical sites and institutional review boards;
- the number of subjects patients required for clinical trials may be larger than we anticipate, such as we experienced with the increase of the target number of enrolled subjects patients for our Phase 2b/3 PRISM trial from 240 to 360 subjects patients as a result of the sample size re-estimation or SSRE, analysis;
- subject enrollment in clinical trials may be slower than we anticipate whether as a result of the COVID-19 pandemic or other outbreaks of infectious disease or otherwise, or participants may discontinue their participation in these clinical tria at a higher rate than we anticipate, as we experienced in our Phase 2b/3 PRISM trial of Haduvio for the treatment of pru nodularis;
- the cost of planned clinical trials may be greater than we anticipate, such as with our Phase 2b/3 PRISM trial where if we added are required to add additional sites, increased increase the target number of enrolled subjects, experienced enrollment that took longer than expected and used patients or use additional incentive strategies to address site activat and enrollment;

- our clinical trials trial sites may not have adequate staff and resources to support our trials on a timely basis;
- our third-party contractors, including any that may be manufacturing a product candidate or drug substance or conductir clinical trials on our behalf, may deviate from applicable trial protocols, fail to comply with regulatory requirements or fail meet their contractual obligations to us in a timely manner or at all;
- regulators or institutional review boards may not authorize us or our investigators to commence a clinical trial or conduc clinical trial at a prospective trial site;
- we may experience delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- subjects patients who enroll in a clinical trial may misrepresent their eligibility to do so or may otherwise not comply with applicable clinical trial protocols, resulting in the need to drop the subjects patients from the clinical trial, increase the needed enrollment size for the clinical trial or extend the clinical trial's duration;
- we may have to delay, suspend or terminate clinical trials for various reasons, including a finding that the participants ar being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of a product candidate;

- regulators or institutional review boards may require that we or our investigators suspend or terminate clinical research various reasons, including noncompliance with regulatory requirements or their standards of conduct, a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristic the product candidate or findings of undesirable effects caused by a chemically or mechanistically similar product or product candidate;
- the FDA or comparable foreign regulatory authorities may disagree with our clinical trial designs or our interpretation of from preclinical studies and clinical trials;
- the FDA or comparable foreign regulatory authorities may fail to approve or subsequently find fault with the manufacturi processes or facilities of third-party manufacturers with which we enter into agreements for clinical and commercial supplies;
- the supply or quality of drug substance for our product candidates or the manufactured product candidate or other mate or drug substances necessary to conduct clinical trials of the product candidate may be insufficient, inadequate or not available at an acceptable cost or we may experience interruptions in supply; supply, such as the difficulties we had in obtaining supply of IV butorphanol, the comparator drug in our HAP study;
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change or landscape of available, approved therapies could change in a manner rendering our clinical data insufficient to obtain marketing approvals; and

- the FDA or comparable foreign regulatory authorities may refuse to accept for substantive review any NDA, MAA or oth comparable foreign regulatory application that we submit for a product candidate or may conclude after review of our da that our application is insufficient to obtain marketing approval of a product candidate.

In addition to the above, the COVID-19 pandemic has previously adversely affected our clinical trial operations worldwide, and such pandemic or other outbreaks of infectious disease could in the future adversely affect our clinical trial operations worldwide, including our ability to recruit and retain principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19 or other infectious diseases. The COVID-19 pandemic has resulted and could in the future also result in further delays in our clinical trials due to prioritization of hospital and medical resources toward the pandemic, restrictions in travel, potential unwillingness of patients to enroll in trials or the inability of patients to comply with clinical trial protocols if quarantines or travel restrictions impede patient movement or interrupt healthcare services. Furthermore, the response to the COVID-19 pandemic may redirect resources of regulators in a way that would adversely impact our ability to progress regulatory approvals. In addition, we may face impediments to regulatory meetings and approvals relating to our clinical trials due to measures intended to limit in-person interactions. While the current trajectory of the COVID-19 pandemic is uncertain, in the future, we may continue to experience adverse impacts on our clinical trial activities, business operations, financial condition, and prospects as a result of the future evolution outbreaks of the virus, infectious disease, among other factors.

If we are required to conduct additional clinical trials or other testing of Haduvio or any future product candidate beyond the trials and testing that we contemplate, we are unable to successfully and timely complete clinical trials or other testing of Haduvio or any future product candidate, the results of these trials or tests are unfavorable, uncertain or are only modestly favorable or there are unacceptable safety concerns associated with the product candidate, we may:

- incur additional unplanned costs, which may exceed the resources that we have available or are able to obtain on reasonable terms;
- experience delays in obtaining marketing approval for the applicable product candidate for several years or more, which could shorten the periods during which we may have the exclusive right to commercialize the product candidate or allow competitors to bring products to market before us;
- fail to obtain marketing approval at all;
- obtain marketing approval for indications or patient populations that are not as broad as we originally intended or desire
- obtain marketing approval with labeling that includes significant use or distribution restrictions or significant safety warni including boxed warnings;
- be subject to additional post-marketing testing or other requirements; or
- be required to remove the product from the market after obtaining marketing approval.

In addition, the FDA's and other regulatory authorities' policies with respect to clinical trials may change and additional government regulations may be enacted. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies governing clinical trials, our development plans may be impacted. For example, in December 2022, with the passage of the Food and Drug Omnibus Reform Act, or FDORA, Congress required

sponsors to develop and submit a diversity action plan for each phase Phase 3 clinical trial or any other “pivotal study” of a new drug or biological product. These plans are meant to encourage the enrollment of more diverse patient populations in late-stage clinical trials of FDA-regulated products. Specifically, actions plans must include the sponsor’s goals for enrollment, the underlying rationale for those goals, and an explanation of how the sponsor intends to meet them. In addition to these requirements, the legislation directs the FDA to issue new guidance on diversity action plans.

Similarly, the regulatory landscape related to clinical trials in the EU E.U. recently evolved. The EU E.U. Clinical Trials Regulation, or CTR, which was adopted in April 2014 and repeals the EU E.U. Clinical Trials Directive, became applicable on January 31, 2022. While the Clinical Trials Directive required a separate clinical trial application, or CTA, to be submitted in each member state, Member State of the E.U., or E.U. Member State, to both the competent national health authority and an independent ethics committee, the CTR introduces a centralized process and only requires the submission of a single application to all member states Member States concerned. The CTR allows sponsors to make a single submission to both the competent authority and an ethics committee in each member state, Member State, leading to a single decision per member state. Member State. The assessment procedure of the CTA has been harmonized as well, including a joint assessment by all member states Member States concerned, and a separate assessment by each member state Member State with respect to specific requirements related to its own territory, including ethics rules. Each member state’s Member State’s decision is communicated to the sponsor via the centralized EU E.U. portal. Once the CTA is approved, clinical study development may proceed. If we are not able to address these changes in existing requirements or the adoption of new requirements or policies governing clinical trials or there are difficulties with the implementation of the CTR process, our development plans may be impacted.

Our failure to successfully and timely complete clinical trials of Haduvio for the treatment of chronic cough in adults with IPF or other chronic cough conditions RCC or for the treatment of prurigo nodularis or of any future product candidate and to demonstrate the efficacy and safety necessary to obtain regulatory approval to market any such product candidates would significantly harm our business and could result in the loss or impairment of our ability to generate revenues and effectuate our business strategy.

Our clinical trials may fail to demonstrate adequately the safety and efficacy of Haduvio or any future product candidates, which would likely prevent or delay regulatory approval and commercialization.

Before obtaining regulatory approvals for the commercial sale of Haduvio or any future product candidate we must demonstrate through lengthy, complex and expensive clinical trials that the product candidate is both safe and effective for use in the target indication. Clinical testing is expensive and can take many years to complete, and its outcome is inherently

uncertain. It is possible that even if Haduvio or any future product candidate has a beneficial effect, that effect will not be detected during clinical evaluation as a result of one or more of a variety of factors, including the size, duration, design, measurements, conduct or analysis of our clinical trials. For example, our Phase 2 clinical trial of Haduvio for the treatment of prurigo nodularis failed to meet its primary endpoint and the number of subjects patients who discontinued treatment prior to the end of the trial had a substantial impact on the results. Conversely, as a result of the same factors, our clinical trials may indicate an apparent positive effect of Haduvio or any future product candidate that is greater than the actual positive effect, if any. Similarly, in our clinical trials we may fail to detect toxicity of, or intolerability caused by, Haduvio or any future product candidate or mistakenly believe that Haduvio or any future product candidate is toxic or not well tolerated when that is not the case after the clinical evaluation is completed. Many pharmaceutical and biotechnology companies have suffered significant setbacks in late-stage clinical trials after achieving positive results in earlier development, and we cannot be certain that we will not face setbacks as we continue our clinical development of Haduvio and develop any other product candidates. It is also possible that any of our development programs could be placed on full or partial clinical hold by regulatory authorities at any point, which would delay and possibly prevent further development of those programs.

In addition, even if the clinical trials we plan are successfully completed and Haduvio or any future product candidate achieves its specified endpoints in such trials, we cannot guarantee that the FDA or foreign regulatory authorities will interpret the results as we do, and more trials could be required before we are able to submit product candidates for marketing approval. For example, patients with prurigo nodularis may have pruritus that is caused by dermatological conditions other than prurigo nodularis and at a meeting with the FDA following the completion of our Phase 2 clinical trial of Haduvio for the treatment of prurigo nodularis, the FDA raised the need to adequately isolate a patient population with pruritus associated with prurigo nodularis for our planned Phase 3 clinical trials. While the inclusion criteria in our Phase 2b/3 PRISM trial require that enrolled subjects not be suffering from any active, uncontrolled dermatoses other than prurigo nodularis, it is possible that the FDA could conclude that this is not sufficient to identify patients suffering from pruritus associated with prurigo nodularis, in which case the FDA could question the overall validity of the results of the trial. To the extent that the results of our clinical trials are not satisfactory to the FDA or foreign regulatory authorities for support of a marketing application, approval of product candidates may be significantly delayed or we may be required to expend significant additional resources, which may not be available to us, to conduct additional trials in support of potential approval of product candidates. For instance, if the FDA does not believe that the results of the Phase 2b/3 PRISM trial are sufficiently supportive of an application for marketing approval, the FDA may require us to conduct another Phase 3 clinical trial in addition to the Phase 2b/3 PRISM trial and the additional Phase 3 clinical trial we believe we need to conduct, which would cause us to incur substantial additional costs and significantly delay our development of Haduvio for the treatment of prurigo nodularis.

Use of patient-reported outcome assessments, or PROs, in our clinical trials and high placebo response rates may delay or impair the development of Haduvio or adversely impact our clinical trials.

Although the primary endpoint in our future clinical trials of Haduvio for the treatment of chronic cough in IPF and RCC will be measured using an objective cough monitor, we have PRO instruments as secondary endpoints that may need to validate a supportive PRO instrument of the primary endpoint. There is not currently a validated PRO instrument that has been accepted for chronic cough indications.

Due In addition, due to the difficulty of objectively measuring pruritus, the assessment of pruritus in clinical trials typically involves the use of PROs. Our clinical trials evaluating the efficacy of Haduvio in pruritus indications, including our Phase 2b/3 PRISM trial, have used PROs as primary endpoints. For example, the primary endpoint of our Phase 2b/3 PRISM trial was the proportion of patients achieving at least a 4-point improvement from baseline with respect to their worst itch at week 14 as measured by the Worst Itch Numerical Rating Scale, or WI-NRS, scores, which is a patient-reported assessment on an 11-point scale from 0 to 10 of the severity of the worst itch experienced in the last 24 hours. PROs have an important role in the development and regulatory approval of treatments for pruritus. However, PROs involve patients' subjective assessments of efficacy, and this subjectivity can increase the uncertainty of clinical trial outcomes assessing pruritus. Such assessments can be influenced by a number of factors and can vary widely from day to day for any particular patient and from patient to patient and site to site within a clinical trial, leading to high variability in PRO measurements.

In addition, although the primary endpoint in our future clinical trials of Haduvio for the treatment of chronic cough in adults with IPF and other chronic cough indications is likely to be measured using an objective cough monitor, we will need to validate a supportive PRO instrument of the primary endpoint. There is not a validated PRO instrument now that has been accepted for chronic cough indications.

In addition, PROs have historically been observed to have high placebo group response rates. We observed this in some of our clinical trials of Haduvio. The variability of PRO measures may be greater than other measures used for clinical trial assessments, and that variability can complicate clinical trial design, adversely impact the ability of a trial to show a statistically significant improvement and generally adversely impact a clinical development program by introducing additional uncertainties.

The variability of PRO measures and related high placebo response rates have adversely impacted clinical results of other therapies being tested and could adversely impact our clinical development of Haduvio. The FDA could also require changes in the PROs we are currently using or indicate that the PROs we are using are insufficient for demonstrating efficacy, potentially delaying clinical development of Haduvio, increasing our costs and making additional clinical trials necessary.

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

We may not be able to initiate or continue clinical trials for Haduvio or any future product candidate if we are unable to locate and enroll a sufficient number of eligible subjects patients to participate in clinical trials as required by the FDA or comparable foreign regulatory authorities. Patient enrollment is a significant factor in the timing of our clinical trials and is affected by many factors, including:

- the size and nature of the eligible patient population;

- the severity of the disease under investigation;
- the proximity of eligible patients to clinical sites;
- patient referral practices of physicians;
- the eligibility criteria for the clinical trial;
- the design of the clinical trial;
- efforts to facilitate timely enrollment;
- competing clinical trials; and
- clinicians' and patients' perceptions as to the potential advantages and risks of the product candidate being studied in relation to other available therapies, including any new drugs that may be approved for the indications under investigatio and
- the impact of the COVID-19 pandemic and other outbreaks of infectious disease, especially in our chronic cough patient population. investigation.

In particular, the successful completion of our clinical development program for Haduvio for the treatment of chronic cough in adults with IPF and RCC and for the treatment of prurigo nodularis is dependent upon our ability to enroll a sufficient number of subjects patients with these severe conditions. We experienced delays and difficulties in the enrollment of subjects patients in our clinical trials, including our Phase 2 CANAL trial and our Phase 2b/3 PRISM trial, which delayed the completion of our trials.

Other companies are conducting clinical trials or have announced plans for future clinical trials that are seeking or are likely to seek to enroll patients with chronic cough associated with IPF, refractory chronic cough RCC or prurigo nodularis, and patients are generally only able to enroll in a single trial at a time. In addition, although there are no drugs No therapies have been approved in the U.S. or Europe to treat for the treatment of chronic cough in adults with IPF and no therapies have been approved in the U.S. or refractory chronic cough, outside the U.S. (with the exception of Japan and Switzerland) for the treatment of RCC. However, patients with these conditions, as well as their physicians, may be reluctant to forgo, discontinue or otherwise alter their use of the therapeutic approaches they currently use in order to participate in our clinical trials. For example, patients may use Dupixent (dupilumab), an injectable prescription medicine, that was approved by the FDA for the treatment of prurigo nodularis in September 2022 or various treatments off-label for the treatment of prurigo nodularis, such as antihistamines or gabapentin; these patients and their physicians may be reluctant to forgo, discontinue or otherwise alter their use of Dupixent or any off-label therapeutic approaches to participate in our clinical trials.

In response to the COVID-19 pandemic, the FDA issued numerous guidance documents and took other actions to facilitate research and development of new drug products. On January 30, 2023, the Biden Administration announced that it will end the public health emergency declarations related to COVID-19 on May 11, 2023. On January 31, 2023, the FDA indicated that it would soon issue a Federal Register notice describing how the termination of the public health emergency will impact the agency's COVID-19 related guidance, including the clinical trial guidance and updates thereto. At this point, it is unclear how, if at all, these developments will impact our efforts to develop and commercialize our product candidates.

Any inability to enroll a sufficient number of subjects patients for our clinical trials could result in significant delays or may require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for Haduvio or any future product candidate, delay or halt the development of and approval processes for such product candidate and jeopardize our ability to commence sales of and generate revenues from such product candidate, any of which could cause the value of our company to decline and limit our ability to obtain additional financing, if needed.

Adverse events or undesirable side effects caused by, or other unexpected properties of, Haduvio or any future product candidate may be identified during development and could delay or prevent the marketing approval or limit the use of Haduvio or any future product candidate.

Adverse events or undesirable side effects caused by or other unexpected properties of, Haduvio or any future product candidate could cause us, an institutional review board or regulatory authorities to interrupt, delay or halt clinical trials of such product candidate and could result in a more restrictive label or the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities. We cannot be certain that serious adverse events or SAEs, will not occur in future clinical trials, which could cause the FDA or comparable foreign regulatory authorities to interrupt, delay or halt clinical trials of such product candidate, approve a more restrictive label than we desire or delay or deny regulatory approval.

In addition, Haduvio, as a mixed κ-opioid receptor agonist and μ-opioid receptor antagonist, may be susceptible to side effects associated with drugs having either of those mechanisms of action. κ-opioid receptor agonists have been associated with poorly tolerated psychiatric side effects, such as feelings of emotional and mental discomfort or dysphoria and hallucinations, at high doses. While we believe that the dual κ-opioid receptor agonist and μ-opioid receptor antagonist mechanism of action of nalbuphine reduces the likelihood of such psychiatric side effects, we have observed mild psychiatric side effects, including a few reported cases of mild euphoria, somnolence and feeling relaxed or feeling "high," in clinical trials of Haduvio to date. μ-opioid receptor antagonists have the potential to precipitate withdrawal effects in patients, including drug addicts. To support our planned submission of an NDA to the FDA for Haduvio, due to the association of opioids with endocrine dysfunction, we may be required to conduct a clinical trial of Haduvio to evaluate potential endocrine side effects. We cannot be certain that any of these side effects often associated with opioids, or other side effects, will not be observed or observed at more severe levels in the future or that the FDA will not require additional trials or impose more severe labeling restrictions due to these side effects or other concerns. Such drug-related side effects could also affect patient recruitment or the ability of enrolled subjects patients to complete a trial or result in potential product liability claims.

In our clinical trials of Haduvio for the treatment of prurigo nodularis, the most frequently reported treatment emergent adverse events associated with Haduvio were nausea, fatigue, dizziness, vomiting, headache, anxiety, depression, constipation and somnolence. In our Phase 2 CANAL trial of Haduvio for the treatment of chronic cough in adults with IPF, the most frequently reported treatment emergent adverse events associated with Haduvio were nausea, fatigue, dizziness, vomiting, headache, constipation and somnolence.

If Haduvio or any future product candidate is associated with adverse events or undesirable side effects or demonstrates unexpected properties, we may need to abandon development or limit development of that product candidate to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Many compounds that have initially shown promise in clinical or earlier stage testing were later discovered to cause undesirable or unexpected side effects or raised other safety issues that delayed or prevented further development of the compound.

The drug label for nalbuphine, the active ingredient in Haduvio, carries an opioid class label warning for serious, life-threatening or fatal respiratory depression.

μ-opioid receptor antagonists such as nalbuphine are associated with respiratory depression. The drug label for nalbuphine, the active ingredient in Haduvio, carries an opioid class label warning for serious, life-threatening or fatal respiratory depression and Haduvio, if approved for marketing in any indication, will likely carry a similar opioid class label. We intend to conduct a Phase 1b study to evaluate the effect of Haduvio to assess the risk of on respiratory depression physiology in patients with IPF. IPF of varying disease severity. We cannot be certain that respiratory depression will not be observed or that the FDA will not require additional trials or impose more severe labeling restrictions related to respiratory depression. If there is a safety signal in the Phase 1b study, it could affect our ability to conduct a trial in this patient population.

Many currently approved μ-opioid products are subject to restrictive marketing and distribution regulations which, if applied to Haduvio, could potentially restrict its use and harm our ability to generate profits.

Many currently approved μ-opioid receptor agonists require a Risk Evaluation and Mitigation Strategy, or REMS, as part of their approval by the FDA. REMS programs may require medication guides for patients, special communication plans to healthcare professionals or elements to assure safe use, such as restricted distribution methods, patient registries and/or other risk minimization tools. While Haduvio has a μ-antagonist mechanism of action and has been well-tolerated in clinical trials to date, we have observed a few cases of mild euphoria, somnolence and feeling relaxed or feeling “high,”

which are characteristics that have led to misuse, abuse and addiction of μ-opioids. We are conducting a HAL HAP study to further characterize compare the abuse potential of oral nalbuphine ER. to IV butorphanol. If the results of the HAL HAP study suggest that Haduvio may carry risks of misuse, abuse or addiction or even if the trial indicates that Haduvio does not carry such risks, the FDA may require us to implement a REMS program in connection with any commercialization of Haduvio. We cannot predict whether a REMS program would be required as part of FDA approval of Haduvio and, if required, what requirements it might entail. Any limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensation of Haduvio, if approved. If a REMS program is required, depending on the extent of the REMS requirements, the program might significantly increase our costs to commercialize Haduvio. Furthermore, risks of Haduvio that are not adequately addressed through a proposed REMS program for Haduvio may also prevent or delay any approval for commercialization.

In addition, the parenteral formulation of nalbuphine is currently not scheduled as a controlled substance under the federal Controlled Substances Act of 1970 or the regulations of the U.S. Drug Enforcement Agency, or the DEA, in the U.S. It is possible that, based on the results of our HAL HAP study, adverse events in our clinical trials or for other reasons, the DEA could determine that Haduvio, which is an oral, extended-release formulation, should be classified as a controlled substance. The DEA regulates controlled substances as Schedule I, II, III, IV or V substances. Schedule I substances by definition have no established medicinal use and may not be marketed or sold in the U.S. A pharmaceutical product may be listed as Schedule II, III, IV or V, with Schedule II substances considered to present the highest risk of abuse and carrying the greater level of regulatory control and Schedule V substances considered to present the lowest relative risk of abuse among such substances and, accordingly, the lowest level of regulatory control. Various states also independently regulate controlled substances. Though state-controlled substance laws often mirror federal law, because the states are separate jurisdictions, they may separately regulate drugs as well. While some states automatically classify a drug when the DEA does so, in other states there must be rulemaking or a legislative action. Regulatory authorities in foreign jurisdictions may also determine to classify Haduvio as a controlled substance under different, but potentially no less burdensome, regulations.

If Haduvio is classified as a controlled substance, the level of regulation would depend on how it is scheduled and we and our suppliers, manufacturers, contractors, distributors and any future customers would be required to obtain and maintain any applicable registrations from state, federal and foreign law enforcement and regulatory agencies and comply with any applicable state, federal and foreign laws and regulations regarding the manufacture, use, sale, importation, exportation and distribution of controlled substances. Also, if Haduvio is classified as a controlled substance, there is a risk that such regulations could limit its supply for use in clinical trials and, in the future, limit our ability to produce and distribute Haduvio in the volume needed to meet potential commercial demand.

Regulations associated with controlled substances govern manufacturing, labeling, packaging, testing, dispensing, production and procurement quotas, record keeping, reporting, handling, shipment and disposal. These regulations increase the personnel needs and the expense associated with development and commercialization of product candidates, including controlled substances. The DEA and some states conduct periodic inspections of registered establishments that handle controlled substances. If Haduvio is classified as a controlled substance, failure to obtain and maintain required registrations or comply with any applicable regulations could delay or preclude us from developing and commercializing Haduvio and subject us to enforcement action. The DEA may seek civil penalties, refuse to renew necessary registrations or initiate proceedings to revoke those registrations. In some circumstances, violations could lead to criminal proceedings. Because of the restrictive nature of these regulations, if Haduvio is classified as a controlled substance, depending on how it is scheduled, its commercial prospects could be limited.

Results of preclinical studies and clinical trials may not be predictive of results of later clinical trials.

The outcome of preclinical studies and clinical trials may not be predictive of the success of later clinical trials and preliminary or interim results of clinical trials do not necessarily predict final results. For instance, Haduvio or any future product candidate may fail to show the desired safety and efficacy in future clinical trials despite demonstrating positive results in preclinical studies or earlier clinical trials. The results of our Phase 2 CANAL trial for the treatment of chronic cough in adults with IPF may not be predictive of the results of future trials of Haduvio for the treatment of chronic cough in adults with IPF or other chronic cough indications, RCC, and the results of our Phase 2b/3 PRISM trial of Haduvio for the treatment of prurigo nodularis may not be predictive of the results of any future clinical trial in prurigo nodularis. Many pharmaceutical and biotechnology companies have suffered significant setbacks in late-stage clinical trials after achieving positive results in earlier stages of clinical development and we could face similar setbacks. Similarly, the design of a clinical trial can determine whether its results will support marketing approval of a product and adjustments in the design of a clinical trial may not be possible once the clinical trial has commenced.

We have limited experience in designing pivotal clinical trials and flaws in the design of a clinical trial could result in significant delays in completing the clinical trial or may require us to abandon the clinical trial altogether or conduct additional clinical trials. Preclinical and clinical data are also often susceptible to varying interpretations and analyses. Many pharmaceutical and biotechnology companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval for those product candidates. Even if we believe that the results of clinical trials for Haduvio or any future product candidate warrant marketing approval, the FDA or comparable foreign regulatory authorities may disagree and may not grant marketing approval of the product candidate.

In addition, some of our data for Haduvio for the treatment of cough and prurigo nodularis is drawn from *post hoc* analyses of data subsets from the Phase 2 CANAL trial and a Phase 2 trial in prurigo nodularis. While we believe these data may be useful in informing the design of future Phase 3 clinical trials for Haduvio, *post hoc* analyses performed after unmasking trial results can result in the introduction of bias and may not be predictive of success in Phase 3 clinical trials.

In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of patient populations, changes in and adherence to dosing regimens and other clinical trial protocols, as well as the rate of discontinuation among clinical trial participants. If we fail to receive positive results in clinical trials of Haduvio or any future product candidate, the development timeline and regulatory approval and commercialization prospects for those product candidates and, correspondingly, our business and financial prospects would be negatively impacted.

Even if Haduvio or any future product candidate receives marketing approval, we or others may later discover that the product is less effective than previously believed or that it causes undesirable side effects that were not previously identified, which could compromise our ability to market the product.

Clinical trials are conducted in carefully defined sets of patients who have agreed to participate in clinical trials. Consequently, it is possible that our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any or alternatively fail to identify undesirable side effects. If, following approval of a product candidate, we or others discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, any of the following adverse events could occur:

- regulatory authorities may withdraw their approval of the product or seize the product;
- we may be required to recall the product, change the way the product is administered or conduct additional clinical trials
- additional restrictions may be imposed on the marketing of or the manufacturing processes for, the product;
- we may be subject to fines, injunctions or the imposition of civil or criminal penalties;

- regulatory authorities may require the addition of labeling statements, such as a “black box” warning or a contraindicatio
- we may be required to create a Medication Guide outlining the risks of the previously unidentified side effects for distribution to patients;
- we could be sued and held liable for harm caused to patients;
- the product may become less competitive; and
- our reputation may suffer.

Any of these events could harm our business and operations and could negatively impact our stock price.

Even if Haduvio or any future product candidate receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success, in which case the market opportunity for Haduvio may be smaller than we estimate and we may not generate significant revenues or become profitable.

We have never commercialized a product and even if Haduvio or any future product candidate is approved by the appropriate regulatory authorities for marketing and sale, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. Physicians are often reluctant to switch their patients from existing therapies even when new and potentially more effective or convenient treatments enter the market and may be reluctant to prescribe opioid-based therapies due to perceived risks of misuse, abuse and addiction. Further, patients often acclimate to their current therapies and do not want to switch unless their physicians recommend changing products or they are required to switch therapies due to lack of reimbursement for existing therapies.

Efforts to educate the medical community and third-party payors on the benefits of Haduvio or any future product candidate may require significant resources and may not be successful. If Haduvio or any future product candidate is approved but does not achieve an adequate level of market acceptance, we may not generate significant revenues and we may not become profitable. The degree of market acceptance of Haduvio or any future product candidate, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy and safety of the product;
- the potential and perceived advantages of the product compared to other therapies;
- the prevalence and severity of any side effects;
- the potential that the DEA could determine that Haduvio should be classified as a controlled substance;
- the clinical indications for which the product is approved;
- whether the product is designated under physician treatment guidelines as a first-, second- or third-line therapy;
- our ability to offer the product for sale at competitive prices;
- the product's convenience and ease of administration;
- the willingness of the target patient population to try and of physicians to prescribe the product;
- limitations or warnings, including distribution or use restrictions contained in the product's approved labeling;
- the strength of sales, marketing and distribution support for the product;
- the approval of other new products for the same indications;
- the timing of market introduction of the product as well as competitive products;
- adverse publicity about the product or favorable publicity about competitive products;
- potential product liability claims;
- changes in the standard of care for the targeted indications for the product; and
- availability and amount of coverage and reimbursement from government payors, managed care plans and other third-p payors.

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

Because we have limited financial and managerial resources, we intend to focus on developing product candidates for specific indications that we identify as most likely to succeed, in terms of both their potential for marketing approval and commercialization. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that may prove to have greater commercial potential. For example, we currently intend to focus our resources on the development of Haduvio for certain indications. However, the development of Haduvio for these indications may ultimately prove to be unsuccessful or less successful than another product candidate or other indications that we might have chosen to pursue with our limited resources.

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 development programs and product candidates 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 the product candidate.

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

We do not currently have a sales, marketing or distribution infrastructure and have no experience in the sale, marketing or distribution of pharmaceutical products. To achieve commercial success for any approved product, we must either develop a sales and marketing organization or outsource these functions to third parties. If Haduvio receives marketing approval from the FDA for chronic cough in adults with IPF, we plan to market and commercialize Haduvio in the U.S. with our own focused, specialty sales organization targeting pulmonologists who specialize in IPF. We would not If Haduvio receives marketing approval from the FDA for other larger chronic conditions, such as RCC or prurigo nodularis, we may plan to market and commercialize Haduvio for other larger conditions such as refractory chronic cough in the U.S. with our own focused, specialty sales organization, or prurigo nodularis. Instead, we would plan to seek to enter into a

strategic alliance for commercialization for such indication or indications. We also expect to utilize a variety of collaboration, distribution and other marketing arrangements with one or more third parties to commercialize Haduvio outside the U.S.

We plan to build focused capabilities to commercialize development programs for certain indications where we believe that medical specialists are sufficiently concentrated to allow us to effectively promote products with a specialty sales team. The development of sales, marketing and distribution capabilities will require substantial resources, will be time-consuming and could delay any product launch. We could prematurely or unnecessarily incur commercialization costs if the commercial launch of a product candidate for which we recruit a sales force and establish marketing and distribution capabilities is delayed or does not occur for any reason. This may be costly, and our business and financial prospects could be significantly affected if we could not retain or reposition our sales and marketing personnel. In addition, we may not be able to hire or retain a sales force in the U.S. that is sufficient in size or has adequate expertise in the medical markets that we plan to target. If we are unable to establish or retain an adequate sales force and marketing and distribution capabilities, our operating results may be adversely affected. If a potential partner has development or commercialization expertise that we believe is particularly relevant to one of our products, then we may seek to collaborate with that potential partner even if we believe we could otherwise develop and commercialize the product independently.

In certain indications and markets, we may seek to enter into collaborations that we believe may contribute to our ability to advance development and ultimately commercialize Haduvio or any future product candidate. We may also seek to enter into collaborations where we believe that realizing the full commercial value of our development programs will require access to broader geographic markets or the pursuit of broader patient populations or indications. As a result of entering into arrangements with third parties to perform sales, marketing and distribution services, our product revenues or the profitability of these product revenues may be substantially lower than if we were to directly market and sell products in those markets. Furthermore, we may be unsuccessful in entering into the necessary arrangements with third parties or may be unable to do so on terms that are favorable to us. In addition, we may have little or no control over such third parties and any of them may fail to devote the necessary resources and attention to sell and market our products effectively.

If we do not establish sales, marketing and distribution capabilities, either on our own or in collaboration with third parties, we will not be successful in commercializing any product candidate that receives marketing approval.

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

The development and commercialization of new products is highly competitive. We expect that we will face significant competition from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide with respect to Haduvio or any future product candidate that we may seek to develop or

commercialize. Our competitors may succeed in developing, acquiring or licensing technologies and products that are more effective, have fewer or more tolerable side effects or are more convenient or less costly than Haduvio or any future product candidate we may develop, which could render any product candidates obsolete and noncompetitive. Our competitors also may obtain FDA or other marketing approval for their products before we are able to obtain approval for ours, which could result in competitors establishing a strong market position before we are able to enter the applicable market.

If Haduvio is approved for the treatment of chronic cough in adults with IPF, we expect that it may compete with product candidates currently in clinical development for the treatment of chronic cough in adults with IPF, such as orvepitant, a NK1 receptor antagonist, which is being developed by Nerre Therapeutics, ME-015, a reactive oxygen species scavenger, which is being developed by Melius Pharma, and ifenprodil, a NMDA receptor antagonist, which is being developed by Algernon Pharmaceuticals. We expect that it might also compete with other product candidates currently in development, or submitted for approval to the FDA, for the treatment of refractory chronic cough and unexplained chronic cough by companies including Merck, Shionogi, Bellus Health, and Genentech. In addition, it is possible that product candidates currently in development for the treatment of IPF could, if approved, reduce the need for therapies to treat chronic cough in adults IPF. We expect that Haduvio might also compete with other product candidates currently in development, or submitted for approval to the FDA, for the treatment of RCC and unexplained chronic cough that might be used off-label to treat chronic cough in IPF.

If Haduvio is approved for the treatment of RCC, we expect that it may compete with product candidates currently in clinical development for the treatment of RCC such as gefapixant, a P2X3 antagonist, which is being developed by Merck, however, in December of 2023 the FDA issued a complete response letter to Merck which concluded that Merck's application did not meet substantial evidence of effectiveness for treating RCC and unexplained chronic cough. On December 20, 2023, Merck announced that it is reviewing the FDA's feedback to determine next steps. Other product candidates that are currently in development for the treatment of RCC include camlipixant, a P2X3 antagonist, which is being developed by GSK plc, NTX-1175, a charged sodium channel blocker, which is being developed by Nocion, GDC-6599, a TRPA1 antagonist, which is being developed by Genentech, ifenprodil, a NMDA receptor antagonist, which is being developed by Algernon Pharmaceuticals, AX-8, a TRPM8 antagonist, which is being developed by Axalbion, and $GABA_B$ PAM, a GABA agonist, which is being developed by Addex Therapeutics.

We also expect that Haduvio would compete with a number of therapeutics that are used off-label to treat chronic cough, including opioids, proton-pump inhibitors, and neuromodulators.

If Haduvio is approved for the treatment of prurigo nodularis, we expect that it would compete with Dupixent (dupilumab), an injectable prescription medicine which was jointly developed by Sanofi and Regeneron, which is approved in the U.S., E.U., Japan, and which was

approved by the FDA China for the treatment of adults with moderate-to-severe prurigo nodularis in September 2022. Sanofi has announced its plans to make regulatory submissions around the world for this indication. nodularis. We also

expect that Haduvio would compete with a number of therapeutics that are used off-label to treat prurigo nodularis, including anti-itch creams and emollients, oral janus kinase, or JAK, receptor inhibitors, and oral or injectable antihistamines. Patients may also try gabapentin and Lyrica (pregabalin), which are prescription medicines approved for the treatment of seizures and neuropathic pain, naltrexone and UVB light therapy. We also expect that Haduvio might compete with product candidates currently in clinical development in this indication, including nemolizumab, an anti-interleukin-31 receptor A humanized monoclonal antibody being developed by Galderma; vixarelimab, a monoclonal antibody targeting oncostatin M receptor beta being developed by Kiniksa Pharmaceuticals; abrocitinib, an oral small molecule targeting the janus kinase 1, or JAK1, receptor being developed by Pfizer Inc.; INCB054707, povorcitinib, an oral small molecule targeting the JAK 1, receptor being developed by Incyte; M1880C, ruxolitinib cream, a topical non-steroidal anti-inflammatory drug, or NSAID, therapy targeting the JAK 1/JAK 2 receptor being developed by Maruho; Incyte; and CDX-0159, barzolvolimab (CDX-0159), a humanized monoclonal antibody targeting the KIT receptor being developed by Celldex Therapeutics. In addition, a number of other product candidates are currently in clinical development to treat other pruritic conditions and Haduvio, if approved for the treatment of prurigo nodularis could face competition from these product candidates, including difelikefalin, an oral kappa opioid receptor agonist being developed by Cara Therapeutics that is initiating Phase 3 clinical trials for chronic pruritus in patients with atopic dermatitis, and in Phase 2 clinical trials for chronic kidney disease, chronic liver disease and notalgia paresthetica.

Many of our competitors and potential competitors, either alone or with their strategic partners, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining marketing approvals and commercializing approved products than we do. Mergers and acquisitions in the pharmaceutical biotechnology and biotechnology pharmaceutical industries 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 companies also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials.

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

The commercial success of any product we develop will depend substantially, both in the U.S. and other countries, on the extent to which the costs of the product will be paid by third-party payors, including government health administration authorities and private health coverage insurers. If coverage and reimbursement are not available or reimbursement is available only to limited levels, we may not be able to successfully commercialize that product. Even if coverage is provided for the product, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a return on our investments. In the U.S., no uniform policy of coverage and reimbursement for

products exists among third-party payors and coverage and reimbursement for products can differ significantly from payor to payor. 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 any product we commercialize to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

There is significant uncertainty related to third-party payor coverage and reimbursement of newly approved drugs. Marketing approvals, pricing and reimbursement for new drug products vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we may obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay commercial launch of the product, possibly for lengthy time periods, which may negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if those product candidates obtain marketing approval.

Patients who are provided medical treatment for their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. Therefore, our ability to commercialize any product candidate will depend in part on the extent to which coverage and reimbursement for these products and related treatments will be available from third-party payors. Third-party payors decide which medications they will cover and establish reimbursement levels. The healthcare industry is acutely focused on cost containment, both in the U.S. and other countries. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications, which could affect our ability to sell products profitably. These payors may not view our products, if any, as cost-effective and coverage and reimbursement may not be available to our customers or may not be sufficient to allow our products, if any, to be marketed on a competitive basis. Cost-control initiatives could cause us to decrease the price we might establish for products, which could result in lower than anticipated product revenues. If the prices for our products, if any, decrease or if governmental and other third-party payors do not provide coverage or adequate reimbursement, our prospects for revenue and profitability will suffer.

The commercial potential of any products we are able to commercialize depends in part on reimbursement by government health administration authorities, private health insurers and other organizations. If we are unable to obtain coverage or reimbursement for those products at the levels anticipated, our financial condition could be harmed. Additionally, if new compounds currently in development by potential competitors obtain marketing approval, there may be downward pressure on reimbursement levels for therapies in our target indications, which could have a negative impact on our ability to achieve and maintain profitability.

There may also be delays in obtaining coverage and reimbursement for newly approved drugs and coverage may be more limited than the indications for which the drug is approved by the FDA or comparable foreign regulatory authorities. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including development, manufacture, sale and distribution. Reimbursement rates may vary, by way of example, according to the use of the product and the clinical setting in which it is used. Reimbursement rates may also be based on reimbursement levels already set for lower cost drugs or may be incorporated into existing payments for other services.

In addition, increasingly, third-party payors are requiring higher levels of evidence of the benefits and clinical outcomes of new therapies and are challenging the prices charged for new products. We cannot be sure that coverage will be available for any product candidate that we commercialize and, if available, that the reimbursement rates will be adequate. Further, the net reimbursement for drug products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the U.S. An inability to promptly obtain coverage and adequate payment rates from both government-funded and private payors for any of our product candidates for which we obtain marketing approval could significantly harm our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

Product liability lawsuits could divert our resources, cause us to incur substantial liabilities and limit commercialization of any products that we may develop or in-license.

We face an inherent risk of product liability claims as a result of our clinical trials, despite obtaining appropriate informed consents from our clinical trial participants. We will face an even greater risk if we commercialize any product that we may develop. For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for any products that we may develop or in-license;

- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend resulting litigation;
- substantial monetary awards to trial participants or patients;

- loss of revenue;
- reduced resources of our management to pursue our business strategy; and
- the inability to commercialize any products that we may develop.

Although we maintain product and clinical trial liability insurance of at least $7.0 million in the aggregate, our insurance coverage may not fully cover potential liabilities that we may incur. The cost of any product or clinical trial liability litigation or other proceeding, even if resolved in our favor, could be substantial. We will need to increase our insurance coverage if we commercialize any product that receives marketing approval. If we are unable to maintain sufficient insurance coverage at an acceptable cost or otherwise protect against potential clinical trial liability or product liability claims, the development and commercial production and sale of Haduvio or any future product candidate could be prevented or inhibited, which could harm our business, financial condition, results of operations and prospects.

Risks Related to Our Dependence on Third Parties

We rely on third parties to conduct our clinical trials. If they do not perform satisfactorily, our business could be harmed.

We do not independently conduct clinical trials of our product candidate. We rely on and expect to continue to rely on third parties, such as contract research organizations, or CROs, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials of Haduvio and any future product candidate that we may develop.

These third parties may terminate their engagements with us under certain circumstances. We may not be able to enter into alternative arrangements or do so on commercially reasonable terms. In addition, there is a natural transition period when a new CRO begins work on a clinical trial. As a result, delays would likely occur, which could negatively impact our ability to meet our expected clinical development timelines and harm our business, financial condition and prospects.

Further, although our reliance on these third parties for clinical development activities limits our control over these activities, we remain responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, as well as applicable legal, regulatory and scientific standards. Moreover, the FDA requires and/or other regulatory authorities require us to comply with standards, commonly referred to as current Good Clinical Practices, or cGCPs, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical trial participants are protected. The FDA enforces and other regulatory authorities enforce these cGCPs through periodic inspections of clinical trial sponsors, principal investigators, clinical trial sites and institutional review boards. If we or our third-party contractors fail to comply with applicable cGCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA and other regulatory authorities may require us to perform additional clinical trials before approving the applicable product candidate, which would delay the marketing approval process. We cannot be certain that, upon inspection, the FDA and other regulatory authorities will determine that any of our clinical trials complies with cGCPs. Similar regulatory requirements apply outside the U.S., including the International Council for Harmonisation of Technical Requirements for the Registration

of Pharmaceuticals for Human Use, or ICH. We are also required to register our clinical trials and post the results of our completed clinical trials on a government-sponsored database, ClinicalTrials.gov, and other registries within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Furthermore, the third parties conducting clinical trials on our behalf are not our employees and except for remedies available to us under our agreements with our contractors, we cannot control whether they devote sufficient time, skill and resources to our ongoing development programs. These third parties may also be impacted by developments in the COVID-19 pandemic or other outbreaks of infectious disease, or government measures taken in response to the pandemic or other such outbreaks, in ways that negatively impact their ability to fulfill their contractual obligations to us in connection with our clinical trials, even if we are not otherwise directly affected by such developments or measures. Additionally, these third parties may have relationships with other commercial entities, including potential competitors, for which they may also be conducting clinical trials or other drug development activities, which could impede their ability to devote appropriate time to our clinical programs. Third parties may not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our protocols. For example, we have terminated clinical investigators from our previous clinical trials due to suspected non-compliance with regulatory requirements. If the third parties on which we rely do not carry out their duties, meet their deadlines or comply with regulatory requirements, we will not be able to, or may be delayed in our efforts to, successfully commercialize Haduvio or any future product candidate. In such an event, our financial results and the commercial prospects for any product candidates that we seek to develop could be harmed, our costs could increase and we may not be able to generate revenues or become profitable.

We contract with third parties for the manufacture, storage, packaging and distribution of Haduvio and other drug product for clinical trials, including a single supplier for the active ingredient in Haduvio and expect to continue to rely on third parties for these services in connection with our future development and commercialization efforts for Haduvio and any future product candidates.

We currently have no manufacturing facilities and a relatively small number of personnel with sufficient experience to oversee the manufacturing process. We rely and plan to continue to rely, on contract manufacturers and other third-party contractors to manufacture, store, package and distribute both drug substance and drug product for our clinical trials. If any of our product candidates receive regulatory approval, we plan to continue to rely upon contract manufacturers and, potentially, collaboration partners, to manufacture commercial quantities of such products. We may be unable to establish any further agreements with contract manufacturers or any other third-party contractors or may fail to do so on acceptable

terms or when needed. Even if we are able to establish agreements with such third-party contractors, reliance on third-party contractors entails additional risks, including:

- manufacturing delays if our third-party contractors experience supply chain-related delays, prioritize the supply of other companies' products over Haduvio or any other drug product needed for our clinical trials or any future product candidat experience supply chain-related delays, such as IV butorphanol for our HAP study, or otherwise fail to satisfactorily perfo according to the terms of the agreements between us and them or if unforeseen events in the manufacturing process ar
- the possible termination or nonrenewal of agreements by our third-party contractors at a time that is costly or inconvenie for us;
- the possible breach by third-party contractors of our agreements with them;
- the failure of third-party contractors to comply with applicable regulatory requirements;
- the possible mislabeling of clinical supplies, potentially resulting in the wrong dose amounts being supplied or active dru placebo not being properly identified;

- the possibility of clinical supplies not being delivered to clinical sites on time, leading to clinical trial interruptions or of dr supplies not being distributed to commercial vendors in a timely manner, resulting in lost sales; and
- the possible misappropriation of our proprietary information, including our trade secrets and know-how.

We do not have long-term supply agreements with any of our contract manufacturers. If any of our existing manufacturers should become unavailable to us for any reason or fail to supply us with the ordered quantities, including as a result of the COVID-19 pandemic or other outbreaks of infectious disease, or government measures taken in response to the pandemic or other such outbreaks, we may incur delays in identifying or qualifying replacement manufacturers or in obtaining replacement supply. Any performance failure on the part of our contract manufacturers or the other third-party contractors that we use to store and distribute drug substance and drug product could be disruptive to our operations and delay clinical development or marketing approval of Haduvio or any future product candidates of ours or commercialization of any resulting products, producing additional losses and depriving us of potential product revenue.

We also rely, and plan to continue to rely, on a single supplier, Mallinckrodt, for nalbuphine hydrochloride drug substance. We do not have agreements in place with Mallinckrodt that guarantee supply quantities or pricing. In October 2020, Mallinckrodt and certain of its subsidiaries filed for bankruptcy protection in the U.S. Bankruptcy Court for the District of Delaware, or the Bankruptcy Court. In February 2022, the Bankruptcy Court approved a settlement of Mallinckrodt's opioid litigation and broader chapter 11 reorganization plan, which was also subject to approval by Irish authorities. On April 27, 2022, the High Court of Ireland confirmed the scheme of arrangement between Mallinckrodt, its creditors and its members under Irish law and ordered that the scheme of arrangement would become effective on the same date that the chapter 11 reorganization plan becomes effective. On June 16, 2022, Mallinckrodt announced that it had completed its reorganization process, emerged from chapter 11 bankruptcy proceedings and completed the Irish examinership proceedings. In August 2023, Mallinckrodt again filed for bankruptcy protection in the Bankruptcy Court and is seeking that court's approval of a second chapter 11 reorganization plan. On October 10, 2023, the Bankruptcy Court confirmed Mallinckrodt's plan of reorganization. On November 14, 2023, Mallinckrodt emerged from bankruptcy. It is currently

uncertain what impact, if any, Mallinckrodt's bankruptcy filing filings and the associated reorganization plan plans may have on its ability to continue supplying nalbuphine hydrochloride drug substance to us. Any significant delay in acquisition, increase in cost or decrease in availability of nalbuphine hydrochloride drug substance could considerably delay the manufacture of Haduvio, which could adversely impact the timing of our current and planned clinical trials and potential regulatory approval and commercialization of Haduvio. Although we are evaluating alternate sources of supply that could satisfy our clinical and commercial requirements for nalbuphine drug substance, we have not qualified any alternate sources and cannot assure you that we would be able to establish relationships with any such sources in a timely fashion, on commercially reasonable terms or at all.

If Haduvio or any future product candidates are approved by any regulatory agency, we will need to enter into agreements with third-party contract manufacturers for the commercial production and distribution of those products. In

addition, we may face competition for access to manufacturing facilities as there may be a limited number of contract manufacturers operating under cGMPs that are able to manufacture any such product. Consequently, we may not be able to reach agreement with third-party manufacturers on satisfactory terms, in a timely manner or at all, which could delay our commercialization efforts.

Third-party manufacturers are required to comply with cGMPs and similar regulatory requirements outside the U.S., such as the ICH. Facilities used by our third-party manufacturers must be approved by the FDA after we submit an NDA and before potential approval of the applicable product candidate. Similar regulations apply to manufacturers of product candidates for use or sale in foreign countries. We do not control the manufacturing process and are completely dependent on our third-party manufacturers for compliance with the applicable regulatory requirements for the manufacture of Haduvio. We expect that we would be similarly dependent on third-party manufacturers of Haduvio at commercial scale or any future product candidate. If our manufacturers cannot successfully manufacture drug substance or drug product that conforms to our specifications or the strict regulatory requirements of the FDA and any applicable foreign regulatory authority, they will not be able to secure the applicable approval for their manufacturing facilities. If these facilities are not approved for commercial manufacture, we may need to find alternative manufacturing facilities, which could result in delays in obtaining approval for the applicable product candidate and any future commercialization efforts.

In addition, our manufacturers are subject to ongoing periodic inspections by the FDA and corresponding state and foreign agencies for compliance with cGMPs and similar regulatory requirements both prior to and following the receipt of marketing approval for any product candidate. Some of these inspections may be unannounced. Failure by any of our manufacturers to comply with applicable cGMPs or other regulatory requirements could result in sanctions being imposed

on us, including fines, injunctions, civil penalties, delays, suspensions or withdrawals of approvals, operating restrictions, seizures or recalls of product candidates, interruptions in supply and criminal prosecutions, any of which could significantly impact the available supplies of Haduvio or any future product candidate and harm our business, financial condition and results of operations.

Our current and anticipated future dependence upon others for the manufacture of Haduvio, any other drug product needed for our clinical trials or any future product candidate may harm our future profit margins and our ability to commercialize any products that receive marketing approval on a timely and competitive basis.

We may seek to establish collaborations and, if we are not able to establish them on commercially reasonable terms, we may have to alter our development and commercialization plans.

While we have not entered into any collaborations to date, we may seek to establish one or more collaborations for the development and commercialization of Haduvio or any future product candidate. Potential collaborators may include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies, biotechnology companies and academic research institutions. If Haduvio receives marketing approval from the FDA for chronic cough in adults with IPF, we plan to market and commercialize Haduvio in the U.S. with our own focused, specialty sales organization targeting pulmonologists who specialize in IPF. We would not If Haduvio receives marketing approval from the FDA for other larger chronic conditions, such as RCC or prurigo nodularis, we may plan to market and commercialize Haduvio for other larger conditions such as refractory chronic cough in the U.S. with our own focused, specialty sales organization, or prurigo nodularis. Instead, we would plan to seek to enter into a strategic alliance for commercialization for such indication or indications. We also expect to utilize a variety of collaboration, distribution and other marketing arrangements with one or more third parties to commercialize Haduvio outside the U.S.

We face significant competition in seeking appropriate collaborators. There have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator’s resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator’s evaluation of a number of factors. Those factors may include the potential differentiation of our product candidates from competing product candidates, design or results of clinical trials, the likelihood of approval by the FDA or comparable foreign regulatory authorities and the regulatory pathway for any such approval, the potential market for the product candidate, the costs and complexities of manufacturing and delivering the product to patients and existing or potential competing products. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available for collaboration and whether such a collaboration could be more attractive than a collaboration with us. Any collaboration agreements that we enter into in the future may also contain restrictions on our ability to enter into other potential collaborations or to develop specified product candidates. We may not be able to negotiate collaborations on a timely basis, on acceptable terms or at all. If we are unable to do so, we may have to curtail the development of the product candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay the potential commercialization of such product

candidate, reduce the scope of any sales or marketing activities or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

If we establish one or more collaborations, all the risks relating to product development, regulatory approval and commercialization described in this Annual Report on Form 10-K would also apply to the activities of any such future collaborators.

If we enter into collaborations with third parties for the development or commercialization of Haduvio or any future product candidate, our prospects with respect to those product candidates will depend in significant part on the success of those collaborations.

We may seek to enter into collaborations with third parties for the development or commercialization of Haduvio or any future product candidate. If we enter into any such collaborations, we would have limited control over the amount and timing of resources that our collaborators will dedicate to the development or commercialization of any such product candidates. Our ability to generate revenues from these arrangements would depend on any future collaborators' abilities to successfully perform the functions assigned to them in these arrangements. In addition, any future collaborators may have the right to abandon research or development projects and terminate applicable agreements, including funding obligations, prior to or upon the expiration of the agreed upon terms.

Collaborations involving a product candidate would pose a number of risks, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaboratio
- collaborators may not perform their obligations as expected;
- collaborators may not pursue development and commercialization of the product candidates under the collaboration or m elect not to continue or renew development or commercialization programs, based on clinical trial results, changes in th collaborators' strategic focus or available funding or external factors, such as an acquisition of the collaborator, that dive resources or create competing priorities;
- collaborators may be involved in a business combination and could decide to delay, diminish or terminate the developm or commercialization of any product candidate licensed by us;

- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or aband a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop or develop with third parties, products that compete directly or indirectly with product candidates under the collaboration;
- collaborators with marketing and distribution rights to one or more products may not commit sufficient resources to the marketing and distribution of such product or products;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferre course of development, might cause delays or termination of the research, development or commercialization of produc candidates, might lead to additional responsibilities for us with respect to product candidates or might result in litigation arbitration, any of which would be time-consuming and expensive;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability or misappropriate our intellectual property or other proprietary information;
- collaborators may engage in misconduct or other improper activities, including non-compliance with regulatory standard and requirements;
- disputes may arise between the collaborators and us regarding ownership of or other rights in the intellectual property generated in the course of the collaborations; and
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all.

Risks Related to Our Intellectual Property

If we fail to comply with our obligations under our existing and any future intellectual property licenses with third parties, we could lose license rights that are critical to our business or owe damages to the licensor of such intellectual property.

We are party to an exclusive license agreement with Endo Pharmaceuticals Inc. under which we have licensed certain patent rights and know-how to develop and commercialize products incorporating nalbuphine hydrochloride in any

formulation, including an extended-release formulation such as Haduvio. We may in the future seek additional licenses from others to develop and commercialize additional product candidates or technologies. These licenses may not provide exclusive rights to use the relevant intellectual property in all desired fields of use and in all territories in which we may wish to develop or commercialize product candidates in the future. It is also possible that we may be unable to obtain additional licenses at a reasonable cost or on reasonable terms, if at all.

Our existing license agreements impose and we expect that future license agreements will impose, various diligence, development and commercialization, milestone payment, royalty and other obligations on us. If we fail to comply with our material obligations under these agreements or if we are subject to a bankruptcy event, the licensor may have the right to terminate the license or convert the license to a non-exclusive license, in which event we may be required to negotiate a new or reinstated license with less favorable terms or would not be able to exclusively market or market at all, products covered by the license. Any termination of our license agreements could have a material adverse impact on our business.

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

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our activities or product candidates may infringe the intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights under any collaborative development relationships;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;

- the inventorship or ownership of inventions and know-how resulting from joint creation or use of intellectual property by licensors and us; and
- the priority of invention of any patented technology.

If disputes over intellectual property that we license prevent or impair our ability to maintain those license arrangements on acceptable terms or at all, we may be unable to successfully develop and commercialize any affected product candidates.

If we are unable to obtain and maintain sufficient patent protection for Haduvio or any future product candidate and the disease indications for which we are developing or may in the future develop, Haduvio or if the scope of the patent protection is not sufficiently broad, competitors could develop and commercialize products similar or identical to such product candidate and our ability to successfully commercialize such product candidate may be adversely affected.

Our success depends in large part on our ability to obtain and maintain patent protection in the U.S. and other countries with respect to Haduvio and any future product candidates and their use for indications for which we are developing or may develop, them in the future. If we do not adequately protect our intellectual property rights, competitors may erode or negate any competitive advantage we may have, which could harm our business and ability to achieve profitability. To protect our proprietary position, we have licensed exclusive rights under patents, prosecuted additional patents and filed patent applications in the U.S. and other countries related to methods of use and formulations of Haduvio.

The patent application and approval process is expensive and time-consuming. We may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost, in a timely manner or at all.

Agreements through which we license patent rights may not give us control over patent prosecution or maintenance, so that we may not be able to control which claims or arguments are presented and may not be able to secure, maintain or successfully enforce necessary or desirable patent protection from those patent rights. We may not have primary control over patent prosecution and maintenance for certain of the patents and patent applications we may license and therefore cannot guarantee that these patents and applications will be prosecuted in a manner consistent with the best interests of our business. We cannot be certain that patent prosecution and maintenance activities by our licensors or other responsible third parties have been or will be conducted in compliance with applicable laws and regulations or will result in valid and enforceable patents. It is possible that defects of form in the preparation or filing of our patents or patent applications may exist or may arise in the future, for example with respect to proper priority claims, inventorship, claim scope or patent term adjustments. adjustments, or PTA. If we, our licensors or any future partners, collaborators, licensors or licensees fail to establish, maintain or protect such patents and other intellectual property rights, such rights may be reduced or eliminated. If our licensors or any future partners, collaborators, licensors or licensees disagree or do not fully cooperate with us as to the

prosecution, maintenance or enforcement of any patent rights, those patent rights could be compromised. We, our licensors and any future partners, collaborators, licensors and licensees may also fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection on them. Therefore, we may miss potential opportunities to strengthen our patent position. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain. No consistent policy regarding the breadth of claims allowed in biotechnology and pharmaceutical patents has emerged to date in the U.S. or in many foreign jurisdictions. In addition, the determination of patent rights with respect to pharmaceutical compounds commonly involves complex legal and factual questions, which in recent years have been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain.

Pending patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until a patent issues from such applications. Assuming the other requirements for patentability are met, currently, the first to file a patent application is generally entitled to the patent. However, prior to March 16, 2013, in the

U.S., the first to invent was entitled to the patent. Publications of discoveries in the scientific literature often lag behind the actual discoveries and patent applications in the U.S. and other jurisdictions are typically not published until 18 months after filing or in some cases not at all. Therefore, we cannot be certain that we were the first to make the inventions claimed in our patents or pending patent applications or that we were the first to file for patent protection of such inventions. Similarly, we cannot be certain that parties from whom we do or may license or purchase patent rights were the first to make relevant claimed inventions or were the first to file for patent protection for them. If third parties have filed patent applications on inventions claimed in our patents or applications on or before March 15, 2013, an interference proceeding in the U.S. can be initiated by such third parties to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. If third parties have filed such applications after March 15, 2013, a derivation proceeding in the U.S. can be initiated by such third parties to determine whether our invention was derived from theirs.

Moreover, because the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, our patents or pending patent applications may be challenged in the courts or patent offices in the U.S. and other countries. There is no assurance that all of the potentially relevant prior art relating to our patents and patent applications has been found. If such prior art exists, it may be used to invalidate a patent or may prevent a patent from issuing from a pending

patent application. For example, such patent filings may be subject to a third-party preissuance submission of prior art to the U.S. Patent and Trademark Office, or USPTO, or to other patent offices around the world. Alternatively or additionally, we may become involved in post-grant review procedures, oppositions, derivation proceedings, reexaminations, inter partes review or interference proceedings, in the U.S. or other countries, challenging patents or patent applications in which we have rights, including patents on which we rely to protect our business. An adverse determination in any such challenge may result in loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical products or product candidates or limit the duration of the patent protection of Haduvio or any future product candidates of ours. In addition, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. Furthermore, while it is our policy to require our employees and contractors who may be involved in the conception or development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, conceives or develops intellectual property that we regard as our own. As a result, the inventorship or ownership of our intellectual property may be challenged in the future.

Changes in either the patent laws or interpretation of the patent laws in the U.S. and other countries may diminish the value of our patents or narrow the scope of our patent protection. In addition, the laws of foreign countries may not protect our rights to the same extent or in the same manner as the laws of the U.S. For example, patent laws in various jurisdictions, including significant commercial markets such as Europe, restrict the patentability of methods of treatment of the human body more than U.S. law does.

Issued patents that we have, may obtain or license may not provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able

to circumvent patents by developing similar or alternative technologies or products in a non-infringing manner. Our competitors may also seek approval to market their own products similar to or otherwise competitive with any products that we are able to develop and commercialize. Alternatively, our competitors may seek to market generic versions of any approved products by submitting abbreviated new drug applications, or ANDAs, to the FDA claiming that patents owned or licensed by us are invalid, unenforceable or not infringed. In these circumstances, we may need to defend or assert our patents or both, including by filing lawsuits alleging patent infringement. In any of these types of proceedings, a court or other agency with jurisdiction may find our patents invalid or unenforceable or find that competitors are competing in a non-infringing manner. Thus, even if we have valid and enforceable patents, these patents still may not provide protection against competing products or processes sufficient to achieve our business objectives.

Pursuant to the terms of our license agreements with third parties, we have the right, but not the obligation, to control enforcement of our licensed patents or defense of any claims asserting the invalidity of these patents. Even if we pursue such enforcement or defense, we will require the cooperation of our licensors and cannot guarantee that we would receive it and on what terms. We cannot be certain that our licensors will allocate sufficient resources or prioritize their or our enforcement of such patents or defense of such claims to protect our interests in the licensed patents. If we cannot obtain patent protection or enforce existing or future patents against third parties, our competitive position and our financial condition could suffer.

If we are unable to protect the confidentiality of our trade secrets, the value of our products could be negatively impacted and our business would be harmed.

In addition to the protection afforded by patents, we also rely on trade secret protection for certain aspects of our intellectual property. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, consultants, independent contractors, advisors, contract manufacturers, suppliers and other third parties. We also enter into confidentiality and invention or patent assignment agreements with employees and certain consultants. Any party with whom we have executed such an agreement may breach that agreement and disclose our proprietary information, including our trade secrets and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming and the outcome is unpredictable. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating the trade secret. Further, if any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent such third party or those to whom they

communicate such technology or information, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our business and competitive position could be harmed.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time-consuming and unsuccessful.

Our competitors may infringe our patents, trademarks, copyrights or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming and divert the time and attention of our management and scientific personnel. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents, in

addition to counterclaims asserting that our patents are invalid or unenforceable or both. In any patent infringement proceeding, there is a risk that a court will decide that one of our patents is invalid or unenforceable, in whole or in part and that we do not have the right to stop the other party from using the invention at issue. There is also a risk that, even if the validity of such patents is upheld, the court will construe the patent's claims narrowly or decide that we do not have the right to stop the other party from using the invention at issue on the grounds that our patent claims do not cover the invention. An adverse outcome in a litigation or proceeding involving one or more of our patents could limit our ability to assert those patents against those parties or other competitors and may curtail or preclude our ability to exclude third parties from making and selling similar or competitive products. Similarly, if we assert trademark infringement claims, a court 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 this case, we could ultimately be forced to cease use of such trademarks.

Even if we establish infringement, the court may decide not to grant an injunction against further infringing activity and instead award only monetary damages, which may or may not be an adequate remedy. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could adversely affect the price of shares of our common stock. Moreover, there can be no assurance that we will have sufficient financial or other resources to file and pursue such infringement claims, which typically last for years and require substantial resources. Even if we ultimately prevail in such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings.

If we are sued for infringing intellectual property rights of third parties, such litigation could be costly and time-consuming, its outcome would be uncertain and it could prevent or delay us from developing or commercializing Haduvio or any future product candidate.

Our commercial success depends, in part, on our ability to develop, manufacture, market and sell products without infringing the intellectual property and other proprietary rights of third parties. Third parties may have U.S. and non-U.S. issued patents and pending patent applications relating to compounds and methods of use for the treatment of the disease indications for which we are developing or may in the future develop, Haduvio or any future product candidate. If any third-party patents or patent applications are found to cover Haduvio or any future product candidate or their methods of

use, we may not be free to manufacture or market the product candidates as planned without obtaining a license, which may not be available on commercially reasonable terms or at all.

There is a substantial amount of intellectual property litigation in the biotechnology and pharmaceutical industries and we may become party to or threatened with, litigation or other adversarial proceedings regarding intellectual property rights with respect to our Haduvio or any future product candidates, including interference proceedings before the USPTO. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to Haduvio or any future product candidate. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that Haduvio or any future product candidate may be accused of infringing. The outcome of intellectual property litigation is subject to uncertainties that cannot be adequately quantified in advance. The pharmaceutical and biotechnology industries have produced a significant number of patents and it may not always be clear to industry participants, including us, which patents cover various types of products or methods of use. The coverage of patents is subject to interpretation by the courts and the interpretation is not always uniform. If we were sued for patent infringement, we would need to demonstrate that our product candidates, products or methods either do not infringe the patent claims of the relevant patent or that the relevant patent claims are invalid or unenforceable and we may not be able to do this. Proving invalidity is difficult. For example, in the U.S., proving invalidity requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents. Even if we are successful in these proceedings, we may incur substantial costs and the time and attention of our management and scientific personnel could be diverted in pursuing these proceedings, which could significantly harm our business and operating results. In addition, we may not have sufficient resources to bring these actions to a successful conclusion.

If we are found to infringe a third-party's intellectual property rights, we could be forced, including by court order, to cease developing, manufacturing or commercializing the infringing product candidate or product. Alternatively, we may be required to obtain a license from such third-party in order to use the infringing technology and continue developing, manufacturing or marketing the infringing product candidate or product. However, we may not be able to obtain any

required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us; alternatively or additionally, it could include terms that impede or eliminate our ability to compete successfully in the commercial marketplace. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing Haduvio or any future product candidate or force us to cease some of our business operations, which could harm our business. Claims that we

have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

Changes to the patent law in the U.S. and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involves both technological and legal complexity and is therefore costly, time-consuming and inherently uncertain. Recent patent reform legislation in the U.S., including the Leahy-Smith America Invents Act, or the America Invents Act, could increase those uncertainties and costs. The America Invents Act was signed into law on September 16, 2011 and many of the substantive changes became effective on March 16, 2013. The America Invents Act reformed U.S. patent law in part by changing the U.S. patent system from a "first to invent" system to a "first inventor to file" system, expanding the definition of prior art and developing a post-grant review system. This legislation changes U.S. patent law in a way that may weaken our ability to obtain patent protection in the U.S. for those applications filed after March 16, 2013.

Further, the America Invents Act created new procedures to challenge the validity of issued patents in the U.S., including post-grant review and inter partes review proceedings, which some third parties have been using to cause the cancellation of selected or all claims of issued patents of competitors. For a patent with an effective filing date of March 16, 2013 or later, a petition for post-grant review can be filed by a third party in a nine-month window from issuance of the patent. A petition for inter partes review can be filed immediately following the issuance of a patent if the patent has an effective filing date prior to March 16, 2013. A petition for inter partes review can be filed after the nine-month period for filing a post-grant review petition has expired for a patent with an effective filing date of March 16, 2013 or later. Post-grant review proceedings can be brought on any ground of invalidity, whereas inter partes review proceedings can only raise grounds of invalidity based on lack of novelty or obviousness using published prior art and patents. These adversarial actions at the USPTO review patent claims without the presumption of validity afforded to U.S. patents in lawsuits in U.S. federal courts and use a lower burden of proof than used in litigation in U.S. federal courts. Therefore, it is generally considered easier for a competitor or third-party to have a U.S. patent invalidated in a USPTO post-grant review or inter partes review proceeding than invalidated in a litigation in a U.S. federal court. If any of our patents are challenged by a third-party in such a USPTO proceeding, there is no guarantee that we or our licensors or collaborators will be successful in defending the patent, which would result in a loss of the challenged patent right to us.

The U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. Additionally, there have been recent proposals for additional changes to the patent laws of the U.S. and other countries that, if adopted, could impact our ability to enforce our patents. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents once obtained. Depending on future actions by the U.S. Congress, the U.S. courts, the USPTO and the relevant law-making bodies in other countries, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future. For example, recent decisions, including by the U.S. Court of Appeals for the Federal Circuit, raise questions regarding the award of PTA for patents in families where related patents have issued without PTA. Thus, it cannot be said with certainty how PTA will/will not be viewed in the future and whether patent expiration dates may be impacted.

Further, in Europe, a new unitary patent system takes took effect June 1, 2023, which will significantly impact impacts European patents, including those granted before the introduction of such a system. Under the unitary patent system, European applications will have the option, upon grant of a patent, of becoming a Unitary Patent which will be subject to the jurisdiction of the Unitary Patent Court, or the UPC. As the UPC is a new court system, there is no precedent for the court, increasing the uncertainty of any litigation. Patents granted before the implementation of the UPC will have the option of opting out of the jurisdiction of the UPC and remaining as national patents in the UPC countries. Patents that remain under the jurisdiction of the UPC will be potentially vulnerable to a single UPC-based revocation challenge that, if successful, could invalidate the patent in all countries who are signatories to the UPC. We cannot predict with certainty the long-term effects of any potential changes.

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

Filing, prosecuting and defending patents on our product candidates in all countries throughout the world would be prohibitively expensive and our intellectual property rights in some countries outside the U.S. are less extensive than those in the U.S. The requirements for patentability may differ in certain countries, particularly in developing countries; thus, even in countries where we do pursue patent protection, there can be no assurance that any patents will issue with claims that cover our products. Our competitors may export otherwise infringing products to territories where we have no patent protection or where we may obtain patent protection, but where patent enforcement is not as strong as that in the U.S. and our issued or licensed patents and any future patent claims or other intellectual property rights may not be effective or sufficient to prevent them from so competing.

Moreover, our ability to protect and enforce our intellectual property rights may be adversely affected by unforeseen changes in foreign intellectual property laws. Additionally, laws of some countries outside of the U.S. and Europe do not afford intellectual property protection to the same extent as the laws of the U.S. and Europe. Many companies have

encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, including India, China and other developing countries, do not favor the enforcement of patents and other intellectual property rights. This could make it difficult for us to stop the infringement of our patents or the misappropriation of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. Consequently, we may not be able to prevent third parties from practicing our inventions in certain countries outside the U.S. and Europe.

In addition, geo-political geopolitical actions in the United States and in foreign countries could increase the uncertainties and costs surrounding the prosecution or maintenance of our patent applications and the maintenance, enforcement or defense of our 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 our 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 from the United States 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.

Agreements through which we license patent rights may not give us sufficient rights to permit us to pursue enforcement of our licensed patents or defense of any claims asserting the invalidity of these patents (or control of enforcement or defense) of such patent rights in all relevant jurisdictions as requirements may vary.

Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, could result in substantial costs and divert our efforts and resources from other aspects of our business. Moreover, such proceedings could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Furthermore, while we intend to protect our intellectual property rights in major markets for any products that we are able to develop, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market any such products. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate.

We may be subject to claims by third parties asserting that our employees or we have misappropriated their intellectual property or claiming ownership of what we regard as our own intellectual property.

Many of our employees and our licensors' employees, including our senior management, were previously employed at universities or at other biotechnology or pharmaceutical companies, including some which may be competitors or potential competitors. Some of these employees, including each member of our senior management, executed proprietary

rights, non-disclosure, non-competition and non-solicitation agreements or similar agreements, in connection with such previous employment. Although we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these employees have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such third-party. Litigation may be necessary to defend against such claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel or sustain damages. Such intellectual property rights could be awarded to a third-party and we could be required to obtain a license from such third-party to commercialize Haduvio or any future product candidate. Such a license may not be available on commercially reasonable terms or at all. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

In addition, while we typically require our employees, consultants and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own, which may result in claims by or against us related to the ownership of such intellectual property. If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to our senior management and scientific personnel.

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

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and applications are required to be paid to the USPTO and various governmental patent agencies outside of the U.S. in several stages over the lifetime of the patents and applications. The USPTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent

application process and after a patent has issued. 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 non-compliance 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, the 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 Haduvio or any future product candidate, our competitive position would be adversely affected.

If we are unable to obtain licenses from third parties on commercially reasonable terms, our business could be harmed.

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

Risks Related to Regulatory Approval and Other Legal Compliance Matters

If the FDA does not conclude that Haduvio for the treatment of chronic cough in adults with IPF or other chronic cough conditions RCC or for the treatment of prurigo nodularis, or any other development program satisfies the requirements under Section 505(b)(2) of the FDCA or if the requirements for such programs are not as we expect, the approval pathway for these programs will likely take significantly longer, cost significantly more and entail significantly greater complications and risks than anticipated and in any case may not be successful.

We have completed our Phase 2b/3 PRISM trial intend to pursue FDA approval of Haduvio for the treatment of prurigo nodularis and we believe we will need to conduct an additional Phase 3 clinical trial of Haduvio for the treatment of prurigo nodularis chronic cough in IPF under the FDA's Section 505(b)(2) regulatory pathway. The Drug Price Competition and Patent Term Restoration Act of 1984 or the Hatch-Waxman Act, added Section 505(b)(2) to the FDCA. Section 505(b)(2) permits the filing of an NDA where at least some of the information required for approval comes from studies that were not conducted by or for the sponsor and for which the sponsor has not received a right of reference, which could expedite the development program for Haduvio by potentially decreasing the amount of preclinical and clinical data that we would need to generate in order to obtain FDA approval. However, while we believe that Haduvio is a reformulation of an existing drug and, therefore, its active moiety will not be treated as a new chemical entity, or NCE, the submission of an NDA under the Section 505(b)(2) regulatory pathway does not preclude the FDA from determining that Haduvio contains an active moiety that is an NCE and, therefore, is not eligible for review under such regulatory pathway.

If the FDA does not allow us to pursue the Section 505(b)(2) or similar regulatory pathway as anticipated, we may need to conduct additional preclinical experiments and clinical trials, provide additional data and information and meet additional standards for regulatory approval. If this were to occur, the time and financial resources required to obtain FDA approval for Haduvio for the treatment of prurigo nodularis chronic cough in IPF and any future product candidates and complications and risks associated with these product candidates, would likely increase significantly. Moreover, our inability to pursue the Section 505(b)(2) regulatory pathway could result in new competitive products reaching the market more quickly than our product candidates, which would likely harm our competitive position and prospects. Even if we are allowed to pursue the Section 505(b)(2) regulatory pathway, our product candidates may not receive the requisite approvals for commercialization.

In addition, notwithstanding the approval of a number of products by the FDA under Section 505(b)(2) over the last few years, certain competitors and others have objected to the FDA's interpretation of Section 505(b)(2). If the FDA's interpretation of Section 505(b)(2) is successfully challenged, the FDA may be required to change its 505(b)(2) policies and practices, which could delay or even prevent the FDA from approving any NDA that we submit under Section 505(b)(2). In addition, the pharmaceutical industry is highly competitive and Section 505(b)(2) NDAs are subject to special requirements designed to protect the patent rights of sponsors of previously approved drugs that are referenced in a Section 505(b)(2) NDA. These requirements may give rise to patent litigation and mandatory delays in approval of our potential future NDAs for up to 30 months depending on the outcome of any litigation. It is not uncommon for a manufacturer of an approved product to file a citizen petition with the FDA seeking to delay approval of or impose additional approval requirements for, pending competing products. If successful, such petitions can significantly delay or even prevent, the approval of the new product. However, even if the FDA ultimately denies such a petition, the FDA may substantially delay approval while it considers and responds to the petition. In addition, even if we are able to utilize the Section 505(b)(2) regulatory pathway for our product candidates, there is no guarantee this would ultimately lead to faster product development or earlier approval.

Moreover, even if our product candidates are approved under the Section 505(b)(2) pathway, the approval may be subject to limitations on the indicated uses for which the products may be marketed or to other conditions of approval or

may contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the products.

Even if we complete the necessary preclinical studies and clinical trials, the regulatory approval process is expensive, time-consuming and uncertain and may prevent us from obtaining approvals for the commercialization

of Haduvio or any future product candidate. As a result, we cannot predict when or if and in which territories, we will obtain marketing approval to commercialize a product candidate.

The research, testing, manufacturing, labeling, approval, selling, marketing, promotion and distribution of products are subject to extensive regulation by the FDA and comparable foreign regulatory authorities. We are not permitted to market Haduvio or any other product candidate in the U.S. until we receive approval of an NDA from the FDA or in other countries until we receive marketing approval from the applicable regulatory authorities outside the U.S. We have not submitted an application for or received marketing approval for any product candidate in the U.S. or in any other jurisdiction. We have limited experience in conducting and managing the clinical trials necessary to obtain marketing approvals, including FDA approval of an NDA.

The process of obtaining marketing approvals, both in the U.S. and other countries, is lengthy, expensive and uncertain. It may take many years, if approval is obtained at all and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to and inspection of manufacturing facilities by, the relevant regulatory authorities. The FDA or other regulatory authorities may determine that Haduvio or any future product candidate is not safe and effective, only moderately effective or has undesirable or unintended side effects, toxicities or other characteristics that preclude our obtaining marketing approval or prevent or limit commercial use. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

In addition, changes in marketing approval policies during the development period, changes in or the enactment or promulgation of additional statutes, regulations or guidance or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. 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 studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

The FDA may also require that NDA submissions for our product candidates include pediatric data. Under the Pediatric Research Equity Act, an NDA, BLA or supplement to an NDA or BLA for certain drugs and biological products must contain data to assess the safety and effectiveness of the drug or biological product in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective, unless the sponsor receives a deferral or waiver from the FDA. The applicable legislation in the E.U. also requires sponsors to either conduct clinical trials in a pediatric population in accordance with a Pediatric Investigation Plan approved by the Pediatric Committee of the European Medicines Agency, or EMA, or to obtain a waiver or deferral from the conduct of these studies by this Committee. For any of our product candidates for which we are seeking regulatory approval in the U.S. or the E.U., we cannot guarantee that we will be able to obtain a waiver or alternatively complete any required studies and other requirements in a timely manner, or at all, which could result in associated reputational harm and subject us to enforcement action.

Any delay in obtaining or failure to obtain required approvals and clearances could negatively impact our ability to generate revenue from the particular product candidate, which likely would result in significant harm to our financial position and adversely impact our stock price.

We have conducted, are conducting and intend in the future to conduct clinical trials for Haduvio and may conduct clinical trials for any future product candidates, at sites outside the U.S. The FDA may not accept data from trials conducted in such locations and the conduct of trials outside the U.S. could subject us to additional delays and expense.

We have conducted, are conducting and intend in the future to conduct clinical trials for Haduvio, and may conduct clinical trials for any future product candidates, at trial sites that are located outside the U.S. Although the FDA may accept data from clinical trials conducted outside the U.S., acceptance of these data is subject to certain conditions imposed by the FDA.

The FDA will not accept foreign study data as support for an application for marketing approval unless the study satisfies certain conditions. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with cGCPs. The FDA must be able to validate the data from the trial, including, if necessary, through an onsite inspection. The trial population must also have a similar profile to 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, except to the extent the disease being studied does not typically occur in the U.S. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will be dependent upon its determination that the trials also complied with all applicable U.S. laws and regulations. There can be no assurance that the FDA will accept data from trials conducted outside of the U.S. If the FDA does not accept the data from any trial that we conduct outside the U.S., it would likely result in the need for additional trials, which would be costly and time-consuming and delay or permanently halt our development of Haduvio or the applicable future product candidate.

In addition, the conduct of clinical trials outside the U.S. could have a significant adverse impact on us. Risks inherent in conducting international clinical trials include:

- clinical practice patterns and standards of care that vary widely among countries;

- non-U.S. regulatory authority requirements that could restrict or limit our ability to conduct our clinical trials;

- administrative burdens of conducting clinical trials under multiple non-U.S. regulatory authority schema;
- foreign exchange rate fluctuations; and
- diminished protection of intellectual property in some countries.

Failure to obtain marketing approval in foreign jurisdictions would prevent Haduvio or any future product candidate from being marketed in other countries. Any marketing approval we are granted in the U.S. would not assure marketing approval in foreign jurisdictions.

In order to market and sell products in the E.U. and other foreign jurisdictions, we must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The marketing approval process outside the U.S. generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the U.S., a product must be approved for reimbursement before the product can be approved for sale in that country. We may not obtain approvals from regulatory authorities outside the U.S. on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions and approval by one regulatory authority outside the U.S. does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. We may file for marketing approvals but not receive necessary approvals to commercialize any products in any market. Obtaining non-U.S. regulatory approvals and compliance with

non-U.S. regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of any product candidates in any country. In addition, if we fail to obtain the non-U.S. approvals required to market products outside the U.S. or if we fail to comply with applicable non-U.S. regulatory requirements, our target markets will be reduced and our ability to realize the full market potential of Haduvio or any future product candidate will be harmed and our business, financial condition, results of operations and prospects may be adversely affected.

Additionally, Further, we could face heightened risks with respect to seeking obtaining marketing approval authorization in the United Kingdom U.K. as a result of the withdrawal of the United Kingdom U.K. from the EU, E.U., commonly referred to as Brexit. The United Kingdom U.K. is no longer part of the European Single Market and European Union E.U. Customs Union. As of January 1, 2021, the MHRA became responsible for supervising medicines and medical devices in Great Britain, comprising England, Scotland and Wales under domestic law, whereas under the

terms of the Northern Ireland will continue to be Protocol, Northern Ireland is currently subject to European Union rules E.U. rules. The U.K. and E.U. have however agreed to the Windsor Framework which fundamentally changes the existing system under the Northern Ireland Protocol. The Protocol, including with respect to the regulation of medicinal products in the U.K. Once implemented, the changes introduced by the Windsor Framework will see the MHRA be responsible for approving all medicinal products destined for the U.K. market (i.e., Great Britain GB and Northern Ireland), and the EMA will rely on no longer have any role in approving medicinal products destined for Northern Ireland.

In addition, foreign regulatory authorities may change their approval policies and new regulations may be enacted. For instance, the Human Medicines Regulations 2012 (SI 2012/1916) (as amended), or E.U. pharmaceutical legislation is currently undergoing a complete review process, in the HMR, as the basis for regulating medicines. The HMR has incorporated into the domestic law context of the body of European Union law instruments governing medicinal products that pre-existed prior to the United Kingdom's withdrawal from the European Union. The MHRA may rely on a decision taken Pharmaceutical Strategy for Europe initiative, launched by the European Commission in November 2020. The European Commission's proposal for revision of several legislative instruments related to medicinal products (potentially reducing the duration of regulatory data protection, revising the eligibility for expedited pathways, etc.) was published on April 26, 2023. The proposed revisions remain to be agreed and adopted by the European Parliament and European Council and the proposals may therefore be substantially revised before adoption, which is not anticipated before early 2026. The revisions may however have a significant impact on the approval of a new marketing authorization via the centralized procedure until December 31, 2023. Any delay in obtaining or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, may force us to restrict or delay efforts to seek regulatory approval pharmaceutical industry and our business in the United Kingdom for our product candidates, which could significantly and materially harm our business. long term.

We expect that we will be subject to additional risks in commercializing any of our product candidates that receive marketing approval outside the U.S., including tariffs, trade barriers and regulatory requirements; economic weakness, including inflation or political instability in particular foreign economies and markets; compliance with tax, employment, immigration and labor laws for employees living or traveling abroad; foreign currency fluctuations, which could result in increased operating expenses and reduced revenue and other obligations incident to doing business in another country; and workforce uncertainty in countries where labor unrest is more common than in the U.S.

A Fast Track designation, grant of Priority Review status or Breakthrough Therapy status by the FDA is not assured and, in any event, may not actually lead to a faster development or regulatory review or approval process and, moreover, would not assure FDA approval of Haduvio or any future product candidate.

We may be eligible for Fast Track designation, Priority Review or Breakthrough Therapy status for specific indications for the product candidates we may develop. If a product candidate is intended for the treatment of a serious or life-threatening disease or condition and the product candidate demonstrates the potential to address unmet medical needs for this disease or condition, the product candidate sponsor may apply for FDA Fast Track designation. If a product candidate offers major advances in treatment, the product candidate sponsor may apply for FDA Priority Review status. Additionally, a product candidate may be designated as a Breakthrough Therapy if it is intended, either alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that

the product candidate may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. The FDA has broad discretion whether or not to grant these designations, so even if we believe a particular product candidate is eligible for such designation or status, the FDA could decide not to grant it. We have received Fast Track designation for the program to develop Haduvio for the treatment of itch in patients with prurigo nodularis, however this designation or any future Fast Track designation for a different indication, Priority Review or

Breakthrough Therapy status designation, may not result in our experiencing a faster development process, review or approval compared to conventional FDA procedures and there is no assurance that the product candidate will be approved by the FDA.

We may seek PRIME Designation in the EU E.U. for Haduvio but we might not receive such designations and, even if we do, such designations may not lead to a faster development or regulatory review or approval process.

In the EU, E.U., we may seek PRIME designation for Haduvio in the future. PRIME is a voluntary program aimed at enhancing the EMA's role to reinforce scientific and regulatory support in order to optimize development and enable accelerated assessment of new medicines that are of major public health interest with the potential to address unmet medical needs. The program focuses on medicines that target conditions for which there exists no satisfactory method of treatment in the EU E.U. or even if such a method exists, it may offer a major therapeutic advantage over existing treatments. PRIME is limited to medicines under development and not authorized in the EU E.U. and the sponsor intends to apply for an

initial marketing authorization application through the centralized procedure. To be accepted for PRIME, a product candidate must meet the eligibility criteria in respect of its major public health interest and therapeutic innovation based on information that is capable of substantiating the claims.

The benefits of a PRIME designation include the appointment of a CHMP rapporteur to provide continued support and help to build knowledge ahead of a marketing authorization application, early dialogue and scientific advice at key development milestones, and the potential to qualify products for accelerated review, meaning reduction in the review time for an opinion on approvability to be issued earlier in the application process. PRIME enables a sponsor to request parallel EMA scientific advice and health technology assessment advice to facilitate timely market access. Even if we receive PRIME designation for any of our product candidates, the designation may not result in a materially faster development

process, review or approval compared to conventional EMA procedures. Further, obtaining PRIME designation does not assure or increase the likelihood of EMA's grant of a marketing authorization.

Even if we obtain marketing approvals for a product, the terms of approvals and ongoing regulation of such product may limit how we manufacture and market the product, which could impair our ability to generate revenue.

Once marketing approval has been granted, an approved product and its manufacturer and marketer are subject to ongoing review and extensive regulation. We would therefore be required to comply with requirements concerning advertising and promotion for any product for which we obtain marketing approval. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved labeling. Thus, we will not be able to promote any products we develop for indications or uses for which they are not approved.

In addition, manufacturers of approved products and those manufacturers' facilities are required to comply with extensive FDA requirements, including ensuring that quality control and manufacturing procedures conform to cGMPs, which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation and reporting requirements. We and our contract manufacturers could be subject to periodic unannounced inspections by the FDA to monitor and ensure compliance with cGMPs.

Accordingly, assuming we receive marketing approval for one or more products, we and our contract manufacturers will continue to expend time, money and effort in a number of areas of regulatory compliance, including manufacturing, production, product surveillance and quality control.

Any regulatory approval to market Haduvio in the U.S. will be limited by indication. If we fail to comply or are found to be in violation of FDA regulations restricting the promotion of Haduvio for unapproved uses, we could be subject to criminal penalties, substantial fines or other sanctions and damage awards.

If our clinical trials are successful, we intend to seek approval to market Haduvio for the treatment of chronic cough in adults with IPF or refractory chronic cough RCC or for the treatment of prurigo nodularis. If we obtain regulatory approval to market Haduvio with an indication statement for the treatment of chronic cough in adults with IPF or refractory chronic cough, RCC, we expect to be prohibited from marketing Haduvio using any promotional claims relating to treatment of cough generally. If we obtain regulatory approval to market Haduvio with an indication statement for the treatment of prurigo nodularis, we expect to be prohibited from marketing Haduvio using any promotional claims relating to treatment of pruritus generally. Marketing of Haduvio may also be limited by regulatory authorities based on use as a monotherapy or adjuvant, concomitant medications, severity of pruritus and other factors.

The regulations relating to the promotion of products for unapproved uses are complex and subject to substantial interpretation by the FDA, EMA, MHRA and other government agencies. In September 2021, the FDA published final regulations which describe the types of evidence that the agency will consider in determining the intended use of a drug product. While we have conducted, or may in the future conduct, clinical trials to evaluate the use of Haduvio to treat cough

conditions other than chronic cough in adults with IPF and pruritic conditions other than prurigo nodularis, Haduvio cannot be promoted for uses other than uses approved in the labeling by the FDA, EMA, MHRA or other applicable regulatory authorities. Physicians may nevertheless prescribe Haduvio off-label to their patients in a manner that is inconsistent with the approved label. We intend to implement compliance and training programs designed to ensure that our sales and marketing practices comply with applicable regulations. Notwithstanding these programs, the FDA or other government agencies may allege or find that our practices constitute prohibited promotion of Haduvio for unapproved uses. We also cannot be sure that our employees will comply with company policies and applicable regulations regarding the promotion of products for unapproved uses.

Notwithstanding the regulatory restrictions on off-label promotion, the FDA and other regulatory authorities allow companies to engage in truthful, non-misleading, and non-promotional scientific communications concerning their products in certain circumstances. For example, in October 2023, the FDA published draft guidance outlining the agency's non-binding policies governing the distribution of scientific information on unapproved uses to healthcare providers. This draft guidance calls for such communications to be truthful, non-misleading, factual, and unbiased and include all information necessary for healthcare providers to interpret the strengths and weaknesses and validity and utility of the information about the unapproved use. In addition, under some relatively recent guidance from the FDA and the Pre-Approval Information Exchange Act, or PIE Act, signed into law as part of the Consolidated Appropriations Act of 2023, companies may also promote information that is consistent with the prescribing information and proactively speak to formulary committee members of payors regarding data for an unapproved drug or unapproved uses of an approved drug. We may engage in these discussions and communicate with healthcare providers, payors and other constituencies in compliance with all applicable laws, regulatory guidance and industry best practices. We will need to carefully navigate the FDA's various regulations, guidance and policies, along with recently enacted legislation, to ensure compliance with restrictions governing promotion of our products.

In recent years, a significant number of pharmaceutical and biotechnology companies have been the target of inquiries and investigations by various federal and state regulatory, investigative, prosecutorial and administrative entities in connection with the promotion of products for unapproved uses and other sales practices, including the Department of Justice and various U.S. Attorneys' Offices, the Office of Inspector General of the Department of Health and Human Services, or the HHS, the FDA, the Federal Trade Commission, or the FTC, and various state Attorneys General offices. These investigations have alleged violations of various federal and state laws and regulations, including claims asserting antitrust violations, violations of the FDCA, the False Claims Act, the Prescription Drug Marketing Act and anti-kickback

laws and other alleged violations in connection with the promotion of products for unapproved uses, pricing and Medicare and/or Medicaid reimbursement. Many of these investigations originate as "*qui tam*" actions under the False Claims Act. Under the False Claims Act, any individual can bring a claim on behalf of the government alleging that a person or entity has presented a false claim or caused a false claim to be submitted to the government for payment. The person bringing a *qui tam* suit is entitled to a share of any recovery or settlement. *Qui tam* suits, also commonly referred to as "whistleblower suits," are often brought by current or former employees. In a *qui tam* suit, the government must decide whether to intervene and prosecute the case. If it declines, the individual may pursue the case alone.

If the FDA or any other governmental agency initiates an enforcement action against us or if we are the subject of a *qui tam* suit and it is determined that we violated prohibitions relating to the promotion of products for unapproved uses, we could be subject to substantial civil or criminal fines or damage awards and other sanctions such as consent decrees and corporate integrity agreements pursuant to which our activities would be subject to ongoing scrutiny and monitoring to ensure compliance with applicable laws and regulations. Any such fines, awards or other sanctions would have an adverse effect on our revenue, business, financial prospects and reputation.

Any product for which we obtain marketing approval in the future could be subject to post-marketing restrictions or withdrawal from the market and we may be subject to substantial penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with any such product following approval.

Any product for which we obtain marketing approval, as well as the manufacturing processes, post-approval studies and measures, labeling, advertising and promotional activities for such product, among other things, will be subject to ongoing requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping. Even if marketing approval of a product is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, including the requirement to implement a REMS.

The FDA may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of a product. The FDA and other agencies, including the Department of Justice, closely regulate and monitor the post-approval marketing and promotion of products to ensure that they are manufactured, marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding off-label use and if we market any product for an indication that is not approved, we may be subject to warnings or enforcement action for off-label marketing. Violation of the FDCA and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription drugs may lead to investigations or allegations of violations of federal and state health care fraud and abuse laws and state consumer protection laws.

In addition, later discovery of previously unknown adverse events or other problems with any product for which we may obtain marketing approval and its manufacturers or manufacturing processes or failure to comply with regulatory requirements, may yield various results, including:

- restrictions on such product, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of the product;

- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;
- withdrawal of the product from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of the product;
- restrictions on coverage by third-party payors;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of the product;

- product seizure; or
- injunctions or the imposition of civil or criminal penalties.

Finally, our ability to develop and market new drug products may be impacted by ongoing litigation challenging the FDA's approval of mifepristone. Specifically, on April 7, 2023, the U.S. District Court for the Northern District of Texas stayed the approval by the FDA of mifepristone, a drug product which was originally approved in 2000 and whose distribution is governed by various conditions adopted under a REMS. In reaching that decision, the district court made a number of findings that may negatively impact the development, approval and distribution of drug products in the U.S. Among other determinations, the district court held that plaintiffs were likely to prevail in their claim that the FDA had acted arbitrarily and capriciously in approving mifepristone without sufficiently considering evidence bearing on whether the drug was safe to use under the conditions identified in its labeling. Further, the district court read the standing requirements governing litigation in federal court as permitting a plaintiff to bring a lawsuit against the FDA in connection with its decision to approve an NDA or establish requirements under a REMS based on a showing that the plaintiff or its members would be harmed to the extent that the FDA's drug approval decision effectively compelled the plaintiffs to provide care for patients suffering adverse events caused by a given drug.

On April 12, 2023, the district court decision was stayed, in part, by the U.S. Court of Appeals for the Fifth Circuit. Thereafter, on April 21, 2023, the U.S. Supreme Court entered a stay of the district court's decision, in its entirety, pending disposition of the appeal of the district court decision in the Court of Appeals for the Fifth Circuit and the disposition of any petition for a writ of certiorari to or the Supreme Court. The Court of Appeals for the Fifth Circuit held oral argument in the case on May 17, 2023 and, on August 16, 2023, issued its decision. The court declined to order the removal of mifepristone from the market, finding that a challenge to the FDA's initial approval in 2000 is barred by the statute of limitations. But the Court of Appeals did hold that plaintiffs were likely to prevail in their claim that changes allowing for expanded access of mifepristone that FDA authorized in 2016 and 2021 were arbitrary and capricious. On September 8, 2023, the Justice Department and a manufacturer of mifepristone filed petitions for a writ of certiorari, requesting that asked the U.S. Supreme Court to review the Court of Appeals' decision. On December 13, 2023, the Supreme Court granted these petitions for writ of certiorari for the Court of Appeals' decision.

Similar restrictions apply to the approval of our products in the EU. E.U. The holder of a marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. These include: compliance with the EU's E.U.'s stringent pharmacovigilance or safety reporting rules, which can impose post-authorization studies and additional monitoring obligations; the manufacturing of authorized medicinal products, for which a separate manufacturer's license is mandatory; and the marketing and promotion of authorized drugs, which are strictly regulated in the EU E.U. and are also subject to EU E.U. Member State laws. The failure to comply with these and other EU E.U. requirements can also lead to significant penalties and sanctions.

Inadequate funding for the FDA, the SEC and other national government agencies, including from government shutdowns or other disruptions to these agencies' operations, could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory and policy changes. Average review times at the agency have fluctuated in recent years as a result. Disruptions at the FDA and other agencies may also slow the time necessary for new product candidates to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. In addition, government funding of the Securities and Exchange Commission, or the SEC, and other government agencies on which our operations may rely, including those that fund research and development activities, is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA, EMA and other agencies may also slow the time necessary for new product candidates drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several in recent years, including in 2018 and 2019, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, future

government shutdowns could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations.

Separately, in response In addition, disruptions may result that are similar to the COVID-19 pandemic. During the COVID-19 pandemic, a number of companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. As In the event of early 2022, a similar public health emergency in the FDA has resumed inspections of domestic and foreign facilities to ensure timely reviews of applications for medical products. However, future, the FDA may not be able to continue its current pace and review timelines could be extended, including where a pre-approval inspection or an inspection of clinical sites is required. Moreover, on January 30, 2023, the Biden administration announced that it will end the public health emergency declarations related to COVID-19 on May 11, 2023. On January 31, 2023, the FDA indicated that it would soon issue a Federal Register notice describing how the termination of the public health emergency will impact the agency's COVID-19 related guidance. At this point, it is unclear how, if at all, these developments will impact our efforts to develop and commercialize our product candidates. extended. Regulatory authorities outside the U.S. have adopted or United States facing

similar circumstances may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic a similar public health emergency and may also experience delays in their regulatory activities.

If a prolonged government shutdown or other disruption occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Future shutdowns or other disruptions could also affect other government agencies such as the SEC, which may also impact our business by delaying review of our public filings, to the extent such review is necessary, and our ability to access the public markets.

Current and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize Haduvio or any future product candidate and may affect the prices we may obtain.

In the U.S. and some foreign jurisdictions, there have been and continue to be a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could, among other things, prevent or delay marketing approval of Haduvio or any future product candidate, restrict or regulate post-approval activities and affect our ability to profitably sell any products for which we obtain marketing approval. We expect that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in

additional downward pressure on the price that we may receive for any approved products. If reimbursement of our products is unavailable or limited in scope, our business could be materially harmed.

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act or collectively the ACA. In addition, other legislative changes have been proposed and adopted since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2031 under the Coronavirus Aid, Relief and Economic Security Act, or the CARES Act. These Medicare sequester reductions were suspended and reduced through the end of June 2022, with the full 2% cut resuming thereafter.

The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Indeed, under current legislation, the actual reductions in Medicare payments may vary up to 4%.

Since enactment of the ACA, there have been and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts for Jobs Act, or TCJA, in 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. Further, on December 14, 2018, in June 2021, the U.S. Supreme Court dismissed a U.S. District Court judge in lawsuit challenging the Northern District of Texas ruled that the individual mandate portion constitutionality of the ACA is an essential and inseverable feature of the ACA and therefore because the mandate was repealed as part of the TCJA, the remaining provisions of the ACA are invalid as well. The U.S. Supreme Court heard this case on November 10, 2020 and on June 17, 2021, dismissed this action after finding that the plaintiffs do not have standing to challenge bring the constitutionality of the ACA. litigation. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results.

The Trump Administration also took executive actions to undermine or delay implementation of the ACA, including directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers or manufacturers of pharmaceuticals or medical devices. On January 28, 2021, however, President Biden revoked those Orders and issued a new Executive Order which directs federal agencies to reconsider rules and other policies that limit Americans' access to health care and consider actions that will protect and strengthen that access. Under this Order, federal agencies are directed to re-examine: policies that undermine protections for people with pre-existing conditions, including complications related to COVID-19; demonstrations and waivers under Medicaid and the ACA that may reduce coverage or undermine the programs, including work requirements; policies that

undermine the Health Insurance Marketplace or other markets for health insurance; policies that make it more difficult to enroll in Medicaid and the ACA; and policies that reduce affordability of coverage or financial assistance, including for dependents.

We expect that these healthcare reforms, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and additional downward pressure on the price that we receive for any approved product and/or the level of reimbursement physicians receive for administering any approved product we might bring to market. Reductions in reimbursement levels may negatively impact the prices we receive or the frequency with which our products are prescribed

---

---

or administered. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. Accordingly, such reforms, if enacted, could have an adverse effect on anticipated revenue from product candidates that we may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and ability to develop or commercialize product candidates.

Current and future legislative efforts may limit the prices for our products, if and when they are licensed for marketing and that could materially impact our ability to generate revenues.

The prices of prescription pharmaceuticals have also been the subject of considerable discussion in the United States. There have been several recent U.S. congressional inquiries, as well as proposed and enacted state and federal legislation designed to, among other things, bring more transparency to pharmaceutical pricing, review the relationship between pricing and manufacturer patient programs and reduce the costs of pharmaceuticals under Medicare and Medicaid. In 2020, President Trump issued several executive orders intended to lower the costs of prescription products and certain provisions in these orders have been incorporated into regulations. These regulations include an interim final rule implementing a most favored nation model for prices that would tie Medicare Part B payments for certain physician-administered pharmaceuticals to the lowest price paid in other economically advanced countries, effective January 1, 2021. That rule, however, has been subject to a nationwide preliminary injunction and, on December 29, 2021, Centers for Medicare & Medicaid Services, or CMS, issued a final rule to rescind it. With issuance of this rule, CMS stated that it will explore all options to incorporate value into payments for Medicare Part B pharmaceuticals and improve beneficiaries' access to evidence-based care.

In addition, in October 2020, HHS and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program or SIP, to import certain prescription drugs from Canada into the United States. The final

rule is currently That regulation was challenged in a lawsuit by the subject Pharmaceutical Research and Manufacturers of ongoing litigation, America, or PhRMA, but at least six the case was dismissed by a federal district court in February 2023 after the court found that PhRMA did not have standing to sue HHS. Nine states (Vermont, Colorado, (Colorado, Florida, Maine, New Hampshire, New Mexico, North Dakota, Texas, Vermont and New Hampshire) Wisconsin) have passed laws allowing for the importation of drugs from Canada with Canada. Certain of these states have submitted Section 804 Importation Program proposals and are awaiting FDA approval. On January 5, 2023, the intent of developing SIPs FDA approved Florida's plan for review and approval by the FDA. Canadian drug importation.

Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The final rule would eliminate the current also creates a new safe harbor for Medicare drug rebates price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and create new manufacturers. Pursuant to court order, the removal and addition of the aforementioned safe harbors for beneficiary point-of-sale discounts were delayed and pharmacy benefit manager, or PBM, service fees. It originally was set to go into effect recent legislation imposed a moratorium on January 1, 2022, but with passage implementation of the rule until January 1, 2026. The Inflation Reduction Act has been of 2022, or the IRA, further delayed by Congress implementation of this rule to January 1, 2032.

On July 9, 2021, President Biden signed Executive Order 14063, which focuses on, among other things, the price of pharmaceuticals. To address these costs, the Order directs the Department of Health and Human Services, or HHS to create a plan within 45 days to combat "excessive pricing of prescription drugs and enhance domestic pharmaceutical supply chains, to reduce the prices paid by the federal government for such drugs, and to address the recurrent problem of price gouging." Thereafter, on September 9, 2021, HHS released its plan to reduce drug prices. The key features of that plan are to: (a) make drug prices more affordable and equitable for all consumers and throughout the health care system by supporting drug price negotiations with manufacturers; (b) improve and promote competition throughout the prescription drug industry by supporting market changes that strengthen supply chains, promote biosimilars and generic drugs, and increase transparency; and (c) foster scientific innovation to promote better healthcare and improve health by supporting public and private research and making sure that market incentives promote discovery of valuable and accessible new treatments.

More recently, on On August 16, 2022, the Inflation Reduction Act of 2022, or IRA, was signed into law by President Biden. The new legislation has implications for Medicare Part D, which is a program available to individuals who are entitled to Medicare Part A or enrolled in Medicare Part B to give them the option of paying a monthly premium for outpatient prescription drug coverage. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the Department of Health and Human Services (HHS) HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years.

Specifically, with respect to price negotiations, Congress authorized Medicare to negotiate lower prices for certain costly single-source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high-cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Part D drugs in 2027, 15 Part B or Part D drugs in 2028, and 20 Part B or Part D drugs in 2029 and

beyond. This provision applies to drug products that have been approved for at least 9 years and biologics that have been licensed for 13 years, but it does not apply to drugs and biologics that have been approved for a single rare disease or condition. Nonetheless, since CMS may establish a maximum price for these products in price negotiations, we would be fully at risk of government action if our products are the subject of Medicare price negotiations. Moreover, given the risk

that could be the case, these provisions of the IRA may also further heighten the risk that we would not be able to achieve the expected return on our drug products or full value of our patents protecting our products if prices are set after such products have been on the market for nine years.

Further, the legislation subjects patients drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated “maximum fair price” under the law or for taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation. The new law also caps Medicare out-of-pocket drug costs at an estimated $4,000 a year in 2024 and, thereafter beginning in 2025, at $2,000 a year. In addition, the IRA potentially raises legal risks with respect to individuals participating in a Medicare Part D prescription drug plan who may experience a gap in coverage if they required coverage above their initial annual coverage limit before they reached the higher threshold, or “catastrophic period” of the plan. Individuals requiring services exceeding the initial annual coverage limit and below the catastrophic period, must pay 100% of the cost of their prescriptions until they reach the catastrophic period. Among other things, the IRA contains many provisions aimed at reducing this financial burden on individuals by reducing the co-insurance and co-payment costs, expanding eligibility for lower income subsidy plans, and price caps on annual out-of-pocket expenses, each of which could have potential pricing and reporting implications.

Accordingly, while it is currently unclear how On June 6, 2023, Merck & Co. filed a lawsuit against the HHS and CMS asserting that, among other things, the IRA’s Drug Price Negotiation Program for Medicare constitutes an uncompensated taking in violation of the Fifth Amendment of the Constitution. Subsequently, a number of other parties, including the U.S. Chamber of Commerce, Bristol Myers Squibb Company, the PhRMA, Astellas, Novo Nordisk, Janssen Pharmaceuticals,

Novartis, AstraZeneca and Boehringer Ingelheim, also filed lawsuits in various courts with similar constitutional claims against the HHS and CMS. We expect that litigation involving these and other provisions of the IRA will be effectuated, we cannot predict continue, with certainty what impact any federal or state health reforms will have on us, but such changes could impose new or more stringent regulatory requirements on our activities or result in reduced reimbursement for our products, any of which could adversely affect our business, results of operations unpredictable and financial condition.

uncertain results. In the E.U., similar political, economic and regulatory developments may affect our ability to profitably commercialize our product candidates, if approved. In markets outside of the U.S. and the E.U., reimbursement and healthcare payment systems vary significantly by country and many countries have instituted price ceilings on specific products and therapies. In many countries, including those of the E.U., the pricing of prescription pharmaceuticals is subject to governmental control and access. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we or our collaborators may be required to conduct a clinical trial that compares the cost-effectiveness of our product to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount or if pricing is set at unsatisfactory levels, our business could be materially harmed.

Any relationships we may have with customers, healthcare providers and professionals and third-party payors, among others, will be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which could expose us to penalties, including criminal sanctions, civil penalties, contractual damages, reputational harm, fines, disgorgement, exclusion from participation in government healthcare programs, curtailment or restricting of our operations and diminished profits and future earnings.

Healthcare providers, physicians and third-party payors will play a primary role in the recommendation and prescription of any products for which we are able to obtain marketing approval. Any arrangements we have with healthcare providers, third-party payors and customers will subject us to broadly applicable fraud and abuse and other healthcare laws and regulations. The laws and regulations may constrain the business or financial arrangements and relationships through which we conduct clinical research, market, sell and distribute any products for which we obtain marketing approval. These include the following:

Anti-Kickback Statute. The federal Anti-Kickback Statute prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, receiving or providing remuneration (including any kickback, bribe or rebate), directly or indirectly, in cash or in kind, to induce or reward or in return for, either the referral of an individual for or the purchase, lease or order of a good, facility, item or service for which payment may be made under a federal healthcare program such as Medicare and Medicaid.

False Claims Laws. The federal false claims and civil monetary penalties laws, including the federal civil False Claims Act, impose criminal and civil penalties, including through civil whistleblower or *qui tam* actions against individuals or entities for, among other things, knowingly presenting or causing to be presented false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or

avoiding, decreasing or concealing an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties.

HIPAA. The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for, among other things, executing a scheme or making materially false statements in connection with the delivery of or payment for health care benefits, items or services. Additionally, HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations

on covered entities and their business associates that perform certain functions or activities that involve the use or disclosure of protected health information on their behalf, including mandatory contractual terms and technical safeguards, with respect to maintaining the privacy, security and transmission of individually identifiable health information.

Transparency Requirements. The 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 report annually to CMS information related to payments or transfers of value made to physicians, other healthcare providers and teaching hospitals, as well as information regarding ownership and investment interests held by physicians and their immediate family members.

Analogous State and Foreign Laws. Analogous state and foreign fraud and abuse laws and regulations, such as state anti-kickback and false claims laws, can apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors and are generally broad and are enforced by many different federal and state agencies as well as through private actions. Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not pre-empted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that any business arrangements we have with third parties and our business generally, will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, individual imprisonment, additional reporting requirements and oversight if we

become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, disgorgement, contractual damages, reputational harm and the curtailment or restructuring of our operations. Defending against any such actions can be costly, time-consuming and may require significant financial and 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. Further, if any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

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 also prohibited in the E.U. The provision of benefits or advantages to physicians is governed by the national anti-bribery laws of E.U. Member States. Infringement of these laws could result in substantial fines and imprisonment.

Payments made to physicians in certain E.U. Member States must be publicly disclosed. Moreover, agreements with physicians often must be the subject of prior notification and approval by the physician's employer, his or her competent professional organization and/or the regulatory authorities of the individual E.U. Member States. These requirements are provided in the national laws, industry codes or professional codes of conduct, applicable in the E.U. Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

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

The collection, use, disclosure, transfer or other processing of personal data, including personal health data, of individuals in the E.U. is governed by the General Data Protection Regulation, or GDPR. The GDPR became effective on May 25, 2018. It imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data; obtaining consent of individuals; providing notice to individuals regarding data processing activities; responding to data subject requests; taking certain measures when engaging third-party processors; notifying data subjects and regulators of data breaches; and implementing safeguards to protect the security and

confidentiality of personal data. The GDPR imposes strict rules on the transfer of personal data to countries outside the E.U., including the U.S. Failure to comply with the requirements of the GDPR may result in fines of up to 20 million euros or four percent of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies and obtain compensation for damages. The GDPR increases our responsibility and potential liability in relation to personal data that

we process and we may be required to change our business practices or put in place additional mechanisms ensuring compliance with the GDPR. This may be onerous and adversely affect our business, financial condition, results of operations and prospects and despite our efforts, there is a risk that we may be subject to fines, litigation and reputational harm in connection with our European activities.

In October 2022, President Biden signed an executive order to implement the E.U.-U.S. Data Privacy Framework, which would serve as a replacement to the E.U.-U.S. Privacy Shield. The European Union initiated the process to adopt an adequacy decision for the E.U.-U.S. Data Privacy Framework in December 2022 and the European Commission adopted the adequacy decision on July 10, 2023. The adequacy decision will permit U.S. companies who self-certify to the E.U.-U.S. Data Privacy Framework to rely on it as a valid data transfer mechanism for data transfers from the E.U. to the U.S. However, some privacy advocacy groups have already suggested that they will be challenging the E.U.-U.S. Data Privacy Framework. If these challenges are successful, they may not only impact the E.U.-U.S. Data Privacy Framework, but also further limit the viability of the standard contractual clauses and other data transfer mechanisms. The uncertainty around this issue has the potential to impact any future business we may have at the international level.

Similar actions are either in place or under way in the U.S. There are a broad variety of data protection laws that are applicable to our activities and a wide range of enforcement agencies at both the state and federal levels that can review companies for privacy and data security concerns based on general consumer protection laws. The Federal Trade Commission FTC and state Attorneys General all are aggressive in reviewing privacy and data security protections for consumers. New laws also are being considered at both the state and federal levels. For example, the FTC has been particularly focused on the unpermitted processing of health and genetic data through its recent enforcement actions and is expanding the types of privacy violations that it interprets to be “unfair” under Section 5 of the Federal Trade Commission Act, as well as the types of activities it views to trigger the Health Breach Notification Rule (which the FTC also has the authority to enforce). The agency is also in the process of developing rules related to commercial surveillance and data security that may impact our business. We will need to account for the FTC’s evolving rules and guidance for proper privacy and data security practices in order to mitigate our risk for a potential enforcement action, which may be costly. If we are subject to a potential FTC enforcement action, we may be subject to a settlement order that requires us to adhere to very specific privacy and data security practices, which may impact our business. We may also be required to pay fines as part of a settlement (depending on the nature of the alleged violations). If we violate any consent order that we reach with the FTC, we may be subject to additional fines and compliance requirements.

In addition, regulations promulgated pursuant to HIPAA establish privacy and security standards that limit the use and disclosure of individually identifiable health information, or protected health information, and require the implementation of

administrative, physical and technological safeguards to protect the privacy of protected health information and ensure the confidentiality, integrity and availability of electronic protected health information. Determining whether protected health information has been handled in compliance with applicable privacy standards and our contractual obligations can be complex and may be subject to changing interpretation. These obligations may be applicable to some or all of our business activities now or in the future.

If we are unable to properly protect the privacy and security of protected health information, we could be found to have breached our contracts. Further, if we fail to comply with applicable privacy laws, including applicable HIPAA privacy and security standards, we could face civil and criminal penalties. HHS enforcement activity can result in financial liability and reputational harm, and responses to such enforcement activity can consume significant internal resources. In addition, state attorneys general are authorized to bring civil actions seeking either injunctions or damages in response to violations that threaten the privacy of state residents. We cannot be sure how these regulations will be interpreted, enforced or applied to our operations. In addition to the risks associated with enforcement activities and potential contractual liabilities, our ongoing efforts to comply with evolving laws and regulations at the federal and state level may be costly and require ongoing modifications to our policies, procedures and systems.

New laws also are being considered at the state level. Most prominently, in California, the California Consumer Privacy Protection Act, or the CCPA, which went into effect on January 1, 2020, created similar risks and obligations as those created amended by GDPR, though the CCPA does exempt certain information collected as part of a clinical trial subject to the Federal Policy for the Protection of Human Subjects (the Common Rule). Additionally, as of January 1, 2023, the California Privacy Rights Act, or the CPRA, will significantly modify which went into effect on January 1, 2023, establishes a privacy framework for covered businesses by creating an expansive definition of personal information, establishing data privacy rights for consumers and employees in the State of California, imposing special rules on the collection of consumer data from minors, and creating a potentially severe statutory damages framework for violations of the CCPA including by expanding consumers' rights with respect and for businesses that fail to certain sensitive personal information. implement reasonable security procedures and practices to prevent data breaches. The CPRA also creates created a new state agency that will be is vested with authority to implement and enforce the CCPA and

---

the CPRA. Many While clinical trial data is currently exempt from the current version of the CCPA, other personal information may be applicable and possible changes to the CCPA may broaden its scope.

In addition to California, at least eleven other states have passed comprehensive privacy laws similar to the CCPA and CPRA. These laws are either in effect or will go into effect sometime before the end of 2026. Like the CCPA and

CPRA, these laws create obligations related to the processing of personal information, as well as special obligations for the processing of “sensitive” data (which includes health data in some cases). Some of the provisions of these laws may apply to our business activities. There are also states that are strongly considering or have already passed comprehensive privacy laws during the 2023 legislative sessions that will go into effect in 2024 and beyond, including New Hampshire and New Jersey. Other states will be considering these laws in the future, and Congress has also been debating passing a federal privacy law. There are also states that are specifically regulating health information that may affect our business. For example, Washington state passed a health privacy law in 2023 that will regulate the collection and sharing of health information, and the law also has a private right of action, which further increases the relevant compliance risk. Connecticut and Nevada have also passed similar laws regulating consumer health data and additional states (including Vermont) are considering similar legislation. A broad range such legislation for 2024. These laws may impact our business activities, including our identification of legislative measures also have been introduced at research patients, relationships with business partners and ultimately the federal level. marketing and distribution of our products.

Accordingly, any failure to comply with federal and state laws (both those currently in effect and future legislation) regarding privacy and security of personal information could expose us to fines and penalties under such laws. There also is the threat of consumer class actions related to these laws and the overall protection of personal data. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our reputation and our business.

Laws and regulations governing any international operations we may have in the future may preclude us from developing, manufacturing and selling certain products outside of the U.S. and require us to develop and implement costly compliance programs.

If we further expand our operations outside the U.S., we will need to dedicate additional resources to comply with U.S. laws regarding international operations and the laws and regulations in each jurisdiction in which we operate and plan to operate. The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering or authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the U.S. to comply with certain accounting provisions requiring us to maintain books and records that accurately and fairly reflect all transactions of the company, including international subsidiaries and to devise and maintain an adequate system of internal accounting controls for international operations.

Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA presents particular challenges in the pharmaceutical industry because in many countries, hospitals are operated by the government and doctors and other hospital employees are considered foreign officials. Certain payments to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions.

Various laws, regulations and executive orders also restrict the use and dissemination outside of the U.S., or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. Further, 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 E.U. The provision of benefits or advantages to physicians is also governed by the national anti-bribery laws, of E.U. Member States, such as the U.K. Bribery Act 2010. Infringement of these laws could result in substantial fines and imprisonment. Payments made to physicians in certain E.U. Member States must be publicly disclosed. Moreover, agreements with physicians often must be the subject of prior notification and approval by the physician's employer, his or her competent professional organization and/or the regulatory authorities of the individual E.U. Member States. These requirements are provided in the national laws, industry codes or professional codes of conduct applicable in the E.U. Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

If we expand our presence outside of the U.S., it will require us to dedicate additional resources to comply with these laws and these laws may preclude us from developing, manufacturing or selling certain products and product candidates outside of the U.S., which could limit our growth potential and increase our development costs.

The failure to comply with laws governing international business practices may result in substantial civil and criminal penalties and suspension or debarment from government contracting. The Securities and Exchange Commission, or SEC

---

also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions.

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 harm 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. From time to time and in the future, our operations may involve the use of hazardous and flammable materials, including chemicals and biological materials and may also produce hazardous waste products. Even if we contract with third parties for the disposal of these materials and waste products, we cannot completely eliminate the risk of contamination or injury resulting from these materials. In the event of contamination or injury resulting from the use or disposal of our hazardous materials, we could be held liable for any resulting damages and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

We maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from workplace and other work-related accidents, but this insurance may not provide adequate coverage against potential liabilities. However, we do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us.

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

Our business and operations would suffer in the event of system failures.

Our computer systems, as well as those of our CROs and other third-party contractors and consultants, are vulnerable to damage from cyber-attacks, computer viruses, unauthorized access, sabotage, natural disasters (including hurricanes), terrorism, war and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our business and development programs. programs, in addition to possibly requiring substantial expenditures of resources to remedy. For example, the loss of preclinical studies or clinical trial data from completed, ongoing or planned trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce data. To the extent any disruption or security breach were to result in a loss of or damage to our data or applications or inappropriate disclosure of personal, confidential or proprietary information, we could also incur liability, our competitive position could be harmed and the development of Haduvio or any future product candidate could be significantly delayed. In addition, we may not have adequate insurance coverage to provide compensation for any losses associated with such events.

In the ordinary course of our business, we directly or indirectly collect and store sensitive data, including intellectual property, confidential information, preclinical and clinical trial data, proprietary business information, personal data and personally identifiable health information of our clinical trial subjects patients and employees, in our data centers and on our networks or on those of third parties. The secure processing, maintenance and transmission of this information is critical to our operations. Despite our security measures, our information technology and infrastructure may be vulnerable to attacks by hackers or internal bad actors or breached due to employee error, a technical vulnerability, malfeasance or other disruptions. Additionally, the risk of a security breach or disruption through cyber-attacks has generally increased as the number, intensity and sophistication of attempted attacks from around the world have increased. Although, to our knowledge, we have not experienced any such material security breach to date, any such breach could compromise our networks and the information stored there could be accessed, publicly disclosed, lost or stolen. Any such access, disclosure or other loss of information could result in legal claims or proceedings, liability under laws that protect the privacy of personal information and significant regulatory penalties and such an event could disrupt our operations, damage our reputation and cause a loss of confidence in us and our ability to conduct clinical trials, which could adversely affect our reputation and delay our clinical development of our product candidates.

If the FDA EMA, MHRA or other comparable foreign regulatory authorities approve generic versions of any of our small molecule investigational future products that receive marketing approval through the NDA pathway, or such

authorities do not grant our such future products appropriate periods of data exclusivity before approving generic versions of those products, the sales of our products, if approved, our sales could be adversely affected.

Once an NDA is approved, the product covered thereby becomes a "reference listed "reference-listed drug" in the FDA's publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly known as the Orange Book.

Manufacturers may seek approval of generic versions of reference listed reference-listed drugs through submission of ANDAs in the United States. In support of an ANDA, a generic manufacturer need not conduct clinical trials to assess safety and efficacy. Rather, the sponsor applicant generally must show that its product has the same active ingredient(s), dosage form, strength, route of administration and conditions of use or labelling labeling as the reference listed reference-listed drug and that the generic version is bioequivalent to the reference listed reference-listed drug, meaning it is absorbed in the body at the same rate and to the same extent. Generic products may

---

be significantly less costly to bring to market than the reference listed reference-listed drug and companies that produce generic products are generally able to offer them at lower prices. Thus, following the introduction of a generic drug, a significant percentage of the sales of any branded product or reference listed reference-listed drug is typically lost to the generic product.

The FDA may not approve an ANDA for a generic product until any applicable period of non-patent exclusivity for the reference listed reference-listed drug has expired. The Federal Food, Drug, and Cosmetic Act, or FDCA, provides a period of five years of non-patent exclusivity for a new drug containing a new chemical entity. entity, or NCE. For the purposes of this provision, an NCE is a drug that contains an active moiety that has previously been approved by the FDA in any other NDA. This interpretation was confirmed with enactment of the Ensuring Innovation Act in April 2021. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. Specifically, in cases where such exclusivity has been granted, an ANDA may not be submitted to the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification that a patent covering the reference listed reference-listed drug is either invalid or will not be infringed by the generic product, in which case the sponsor applicant may submit its application four years following approval of the reference listed reference-listed drug. The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical trials, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application.

Generic drug manufacturers may seek to launch generic products following the expiration of any applicable exclusivity period we obtain if our products product candidates are approved, even if we still have patent protection for such products. product candidates. Competition that our products could any such product candidates of ours may face from generic versions of our such products could materially and adversely affect impact our future revenue, profitability and cash flows and substantially limit our ability to obtain a return on the investments we have made may make in those product candidates.

Artificial intelligence presents risks and challenges that can impact our business including by posing security risks to our confidential information, proprietary information and personal data.

Issues in the use of artificial intelligence, combined with an uncertain regulatory environment, may result in reputational harm, liability or other adverse consequences to our business operations. As with many technological innovations, artificial intelligence presents risks and challenges that could impact our business. Our vendors may incorporate generative artificial intelligence tools into their offerings without disclosing this use to us, and the providers of these generative artificial intelligence tools may not meet existing or rapidly evolving regulatory or industry standards with respect to privacy and data protection and may inhibit our or our vendors' ability to maintain an adequate level of service and experience. If any of our vendors experiences an actual or perceived breach or privacy or security incident because of the use of generative artificial intelligence, we may lose valuable intellectual property and confidential information and our reputation and the public perception of the effectiveness of our security measures could be harmed. Further, bad actors around the world use increasingly sophisticated methods, including the use of artificial intelligence, to engage in illegal activities involving the theft and misuse of personal information, confidential information and intellectual property. Any of these outcomes could damage our reputation, result in the loss of valuable property and information, and adversely impact our business.

Risks Related to Employee Matters and Managing our Growth

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

We are highly dependent on Jennifer Good, our President and Chief Executive Officer; Thomas Sciascia, M.D., our Chief Scientific Officer; and David Clark, M.D., MRCP, our Chief Medical Officer; as well as the other principal members of our management and scientific teams. Although we have formal employment agreements with Ms. Good and Dr. Sciascia, these agreements do not prevent them from terminating their employment with us at any time. Except as otherwise required by law, all members of our executive team are employed "at will," meaning that they may terminate their employment with us at any time with or without notice and for any reason or no reason. The loss of the services of any of these persons could impede the achievement of our research, development and commercialization objectives.

Our ability to compete in the biotechnology and pharmaceuticals industries depends upon our ability to attract and retain highly qualified scientific, clinical, manufacturing and sales and marketing personnel. Our industry has experienced a high rate of turnover of such personnel in recent years. If we lose one or more of our executive officers or other key employees, our ability to implement our business strategy successfully could be seriously harmed. Furthermore, replacing

executive officers or other 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 develop, gain marketing approval of and commercialize products successfully. Competition to hire from this limited pool is intense and we may be unable to hire, train, retain or motivate these additional key employees 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.

We rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by other entities and may have commitments under consulting or advisory contracts with those entities that may limit their availability to us. If we are unable to continue to attract and retain highly qualified personnel, our ability to develop and commercialize Haduvio or any future product candidate will be limited.

We expect to If we expand our organization, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

As of December 31, 2022 December 31, 2023, we had 25 employees. We may experience significant growth in the number of our employees and the scope of our operations. For example, if any product candidate appears likely to receive marketing approval, we expect to significantly expand our sales, marketing and distribution capabilities to support the potential commercialization of the product candidate. Our management may need to devote a significant amount of its attention to managing these growth activities. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion of our operations, retain key employees or identify, recruit and train additional qualified personnel. Our inability to manage the expansion of our operations effectively may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Any significant growth could also require significant capital expenditures and may divert financial resources from other projects, such as the development of Haduvio for additional indications or the development of additional product candidates. If we are unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate revenues

could be reduced and we may be unable to implement our business strategy, including the successful commercialization of any product candidate.

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

We are exposed to the risk that our employees, independent contractors and consultants may engage in fraud or other misconduct, including intentional failures to comply with FDA regulations or similar regulations of comparable non-U.S. regulatory authorities, to provide accurate information to the FDA or comparable non-U.S. regulatory authorities, to comply with manufacturing standards we have established, to comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable non-U.S. regulatory authorities, to report financial information or data accurately or to disclose unauthorized activities to us. Such misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter misconduct and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws, standards or regulations. If any such actions are instituted against us and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant criminal, civil and administrative sanctions including monetary penalties, damages, fines, disgorgement, individual imprisonment, exclusion from participation in government funded healthcare programs, such as Medicare and Medicaid, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, reputational harm and requirements to curtail or restructure our operations.

Risks Related to Our Common Stock

An active trading market for our common stock may not be sustainable.

Our shares of common stock began trading on the Nasdaq Global Market, or Nasdaq, on May 7, 2019. Given the limited trading history of our common stock, there is a risk that an active trading market for our shares will not be sustained, which could put downward pressure on the market price for our common stock and thereby affect the ability of our stockholders to sell their shares. An inactive trading market may also impair our ability to raise capital to continue to fund operations by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

If we fail to comply with the continued listing requirements of Nasdaq, our common stock may be delisted and the price of our common stock and our ability to access the capital markets could be negatively impacted.

Our common stock is currently listed for trading on Nasdaq. We must satisfy Nasdaq's continued listing requirements, including, among other things, a minimum closing bid price of $1.00 per share, or risk delisting, which would have a material adverse effect on our business. A delisting of our common stock from Nasdaq could materially reduce the liquidity of our common stock and result in a corresponding material reduction in the price of our common stock. In addition, delisting could harm our ability to raise capital through alternative financing sources on terms acceptable to us, or at all, and may result in the potential loss of confidence by investors, suppliers, customers and employees and fewer business development opportunities.

On January 10, 2022, we received a deficiency letter from the Listing Qualifications Department, or the Staff, of Nasdaq notifying us that, for the prior 30 consecutive business days, the bid price for our common stock had closed below the $1.00 per share minimum bid price requirement for continued inclusion on Nasdaq pursuant to Nasdaq Listing Rule 5450(a)(1), or the Bid Price Requirement.

In accordance with Nasdaq Listing Rule 5810(c)(3)(A), or the Compliance Period Rule, we were provided a period of 180 calendar days, or until July 11, 2022, or the Compliance Date, to regain compliance with the Bid Price Requirement. If, at any time before the Compliance Date, the bid price for our common stock closed at $1.00 or more for a minimum of 10 consecutive business days as required under the Compliance Period Rule, the Staff would provide written notification to us that we had regained compliance with the Bid Price Requirement, unless the Staff chose to exercise its discretion to extend this ten-day period pursuant to Nasdaq Listing Rule 5810(c)(3)(H).

On March 16, 2022, we received a letter from the Staff indicating that, as a result of an increase in our stock price, we had regained compliance with the Bid Price Requirement as of such date.

Although we were able to regain compliance with the Bid Price Requirement within the manner and time period prescribed by Nasdaq, there can be no assurance that we will be able to maintain compliance with the Bid Price

Requirement or other Nasdaq continued listing requirements in the future or that we will be able to regain compliance with respect to any future deficiencies. If we fail to satisfy the Nasdaq Global Market's continued listing requirements, we may submit an application to transfer to the Nasdaq Capital Market, which generally has lower financial requirements for initial listing, in an effort to avoid delisting. However, we may not be able to satisfy the initial listing requirements for the Nasdaq Capital Market and may therefore not be able to transfer our listing to the Nasdaq Capital Market. A transfer of our listing to the Nasdaq Capital Market could adversely affect the liquidity of our common stock. Any such event could make it more difficult to dispose of, or obtain accurate quotations for the price of, our common stock, and there also would likely be a reduction in our coverage by securities analysts and the news media, which could cause the price of our common stock to decline further. We may also face other material adverse consequences in such event, such as negative publicity, a decreased ability to obtain additional financing, diminished investor and/or employee confidence, and the loss of business development opportunities, some or all of which may contribute to a further decline in our stock price.

The trading price of our common stock is highly volatile, which could result in substantial losses for purchasers of our common stock.

The trading price of our common stock is highly volatile. The stock market in general and the market for smaller pharmaceutical and biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. The trading price for our common stock may be influenced by many factors, including:

- the timing and results of clinical trials of Haduvio or any future product candidates;
- the success of existing or new competitive products or technologies;
- regulatory actions with respect to Haduvio or any future product candidates or competitors' products and product candidates;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures, collaborations capital commitments;
- commencement or termination of collaborations for our development programs;
- failure or discontinuation of any of our development programs;
- results of clinical trials of product candidates of our competitors;
- regulatory or legal developments in the U.S. and other countries;
- developments or disputes concerning patent applications, issued patents or other intellectual property rights;
- recruitment or departure of key personnel;
- expenses related to any of our development programs;
- results of our efforts to discover, develop, acquire or in-license additional product candidates;

- actual or anticipated changes in estimated financial results or development timelines;
- announcements or expectations of additional financing efforts;
- sales of our common stock by us, our insiders or other stockholders;
- expiration of market stand-off or lock-up agreements;
- variations in our financial results or those of companies that are perceived to be similar to us;
- recommendations and changes in estimates or recommendations by securities analysts, if any, that cover our stock;
- changes in the structure of healthcare payment systems in the U.S. and other countries;

- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions, including recent adverse changes in the domestic and international financial markets and the impacts of the COVID-19 pandemic or other outbreaks of infectious disease, and the impacts rising inflation and government action in response thereto;
- our obligations in connection with the SVB Term Loan;
- our ability to maintain our listing on the Nasdaq Global Market;

- our ability to continue as a going concern; and
- other factors and considerations described in this “Risk Factors” section.

In addition, the COVID-19 pandemic, rising inflation and interest rate increases and other factors have negatively affected, and may in the future negatively affect, the stock market and investor sentiment. The price and volatility of our common stock may be disproportionately affected as investors may favor traditional profit-making industries and companies during such times of market uncertainty and instability.

We could be subject to securities class action litigation.

In the past, securities class action litigation has often been brought against public companies following declines in the trading prices of their securities. This risk is especially relevant for us because companies in the life sciences space have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management’s attention and our resources, which could harm our business.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, the trading price and volume of our shares could decline.

The trading market for our common stock will likely depend in part on the research and reports that securities or industry analysts publish about us and our business. We do not have any control over these analysts. There can be no assurance that analysts will cover us or provide favorable coverage. If one or more analysts downgrade our stock or change their opinion of our stock, the trading price of our shares would likely decline. In addition, if one or more analysts cease coverage of us or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause the trading price and volume of our shares to decline.

Future sales of shares of our common stock, including by us, employees and significant stockholders, could negatively affect our stock price.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales or the perception in the market that the holders of a large number of shares of our common stock intend to sell their shares, could reduce the trading price of our common stock.

All of our outstanding shares of common stock may be freely sold in the public market at any time to the extent permitted by Rules 144 and 701 under the Securities Act of 1933, as amended, or the Securities Act, or to the extent that such shares have already been registered under the Securities Act and are held by non-affiliates of ours.

Moreover, holders of a substantial number of shares of our common stock have rights, subject to specified limitations and conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders.

In addition, we have registered all shares of common stock that we may issue under our equity compensation plans. These shares can be freely sold in the public market upon issuance and once vested, subject to volume limitations applicable to affiliates. If these additional shares are sold or if it is perceived in the market that they will be sold, in the public market, the trading price of our common stock could decline.

We currently have on file

In June 2023, we filed with the SEC a universal shelf registration statement on Form S-3, or the Shelf Registration Statement, which allows us to offer and sell registered up to $200.0 million of common stock, preferred stock, debt securities, units and/or warrants from time to time pursuant to one or more offerings at prices and terms to be determined at the time of sale. We are The Shelf Registration Statement was filed to replace our prior universal shelf registration statement on Form S-3, or the Prior Shelf Registration Statement. The Shelf Registration Statement was declared effective on August 15, 2023. In June 2023, we entered into a party to an new sales agreement, or the 2023 ATM Sales Agreement, with Leerink Partners and filed a prospectus under our Shelf Registration Statement for the offer and sale of shares of our common stock having an aggregate offering price of up to $75.0 million pursuant to the 2023 ATM Sales Agreement. In accordance with the terms of the 2023 ATM Sales Agreement, our prior ATM sales agreement terminated upon effectiveness of the Shelf Registration Statement, at which from point we were no longer able to issue and sell shares of our common stock under our prior ATM sales agreement. From time to time, we may offer and sell under the 2023 ATM Sales Agreement up to $62.0 million of the common stock registered under the Shelf Registration Statement pursuant to one or more “at-the-market” offerings. As of December 31, 2022, we had sold 3,583,394 shares of common stock for an aggregate purchase price of $11.0 million, before deducting estimated commissions and allocated fees of $0.8 million, pursuant to the ATM Sales Agreement. The extent to which we utilize the 2023 ATM Sales Agreement as a source of funding will depend on a number of factors, including the prevailing market price of our common stock, general market conditions and the extent to which we are able to secure funds from other sources.

On October 5, 2021, we issued to a single investor in a private placement, or the Initial Private Placement Investor, (i) 2,373,201 shares of our common stock and accompanying warrants to purchase an aggregate of 4,746,402 shares of our common stock, and (ii) pre-funded warrants to purchase up to an aggregate of 4,926,069 shares of our common stock and accompanying warrants to purchase an aggregate of 9,852,138 shares of our common stock. Under the terms of the pre-funded warrants and the accompanying common stock warrants, we may not effect the exercise of any such warrant, and

the Initial Private Placement Investor will not be entitled to exercise any portion of any such warrant, if, upon giving effect to such exercise, the aggregate number of shares of common stock beneficially owned by the Initial Private Placement Investor, together with its affiliates, would exceed 4.99%, for the accompanying common stock warrants, or 9.99%, for the

pre-funded warrants, of the number of shares of common stock outstanding immediately after giving effect to the exercise, as such percentage ownership is determined in accordance with the terms of such warrant, which percentage may be increased or decreased at the Initial Private Placement Investor's election upon 61 days' notice to us, subject to the terms of such warrants, provided that such percentage may in no event exceed 9.99%. We refer to such percentage limitations as the Initial Private Placement Beneficial Ownership Limitations. We filed a registration statement on Form S-3, or the Initial Private Placement Form S-3, covering the resale of up to 21,897,810 shares of common stock, comprised of the 2,373,201 shares of common stock issued outright and the 19,524,609 shares of common stock issuable upon exercise of the warrants, which was declared effective in October 2021. While the Initial Private Placement Form S-3 covers the resale of the number of shares of common stock issued or issuable to the Initial Private Placement Investor without giving effect to the Initial Private Placement Beneficial Ownership Limitations, the Initial Private Placement Investor may not exercise, and subsequently resell the underlying shares of common stock of, any portion of the warrants to the extent such exercise would result in the Initial Private Placement Investor exceeding the applicable Initial Private Placement Beneficial Ownership Limitation. The Initial Private Placement Investor may resell all, some or none of the shares of common stock registered pursuant to the Initial Private Placement Form S-3 at any time or in its discretion, subject to the Initial Private Placement Beneficial Ownership Limitations. As of March 16, 2023 March 20, 2024, 6,000,000 of the warrants to purchase shares of common stock issued to the Initial Private Placement Investor to purchase 6,000,000 shares of common stock remained outstanding.

Similarly, on October 18, 2021, we issued to New Enterprise Associates 16, L.P., or NEA, in a private placement, 1,851,852 shares of our common stock and accompanying warrants to purchase an aggregate of 3,703,704 shares of our common stock. We filed a registration statement on Form S-3, or the Second Private Placement Form S-3, covering the resale of 5,555,556 shares of common stock, comprised of the 1,851,852 shares of common stock and the 3,703,704 shares of common stock issuable upon exercise of the warrants, which was declared effective in November 2021. NEA will be able to resell all, some or none of the shares of common stock registered pursuant to the Second Private Placement Form S-3 at any time or in its discretion. As of March 16, 2023 March 20, 2024, all of the warrants issued to NEA remained outstanding.

Similarly, on April 11, 2022, we issued to several purchasers in a private placement, or the April 2022 Private Placement, (i) an aggregate of 4,580,526 shares of our common stock and (ii) pre-funded warrants to purchase an aggregate of 24,379,673 shares of our common stock. Under the terms of the pre-funded warrants, we may not effect the exercise of any such warrant, and a purchaser will not be entitled to exercise any portion of any such warrant, if, upon giving effect to such exercise, the aggregate number of shares of common stock beneficially owned by such purchaser (together with its affiliates, any other persons acting as a group together with such purchaser or any of such purchaser's affiliates, and any other persons whose beneficial ownership of common stock would or could be aggregated with such

purchaser's for purposes of Section 13(d) or Section 16 of the Exchange Act) would exceed 9.99% of the number of shares of common stock outstanding immediately after giving effect to the exercise, as such percentage ownership is determined in accordance with the terms of such warrant, which percentage may be increased or decreased at such purchaser's election upon 61 days' notice to us subject to the terms of such warrants, provided that such percentage may in no event exceed 19.99%. We refer to such percentage limitations as the 2022 Private Placement Beneficial Ownership Limitations. We filed a registration

---

statement on Form S-3, or the Third Private Placement Form S-3, covering the resale of 28,960,199 shares of common stock, comprised of the 4,580,526 shares of common stock and the 24,379,673 shares of common stock issuable upon exercise of the warrants, which was declared effective in May 2022. While the Third Private Placement Form S-3 covers the resale of the number of shares of common stock issued or issuable to the purchasers without giving effect to the 2022 Private Placement Beneficial Ownership Limitations, a purchaser may not exercise, and subsequently resell the underlying shares of common stock of, any portion of the warrants to the extent such exercise would result in such purchaser exceeding the applicable 2022 Private Placement Beneficial Ownership Limitation. The purchasers will be able to resell all, some or none of the shares of common stock registered pursuant to the Third Private Placement Form S-3 at any time or in their discretion, subject to the 2022 Private Placement Beneficial Ownership Limitations. As of March 16, 2023 March 20, 2024, all of the pre-funded warrants that we issued to purchasers and sold in the April 2022 Private Placement to purchase 17,282,760 shares of common stock remained outstanding.

Finally, on September 27, 2022, we issued in the September 2022 Offering and sold an aggregate of 14,252,670 shares of our common stock, and, in lieu of common stock to certain investors, pre-funded warrants to purchase 14,247,330 shares of common stock. stock, in a public offering, or the September 2022 Offering. Under the terms of the pre-funded warrants, we may not effect the exercise of any such warrant, and a purchaser will not be entitled to exercise any portion of any such warrant, if, upon giving effect to such exercise, the aggregate number of shares of common stock beneficially owned by such purchaser (together with its affiliates, any other persons acting as a group together with such purchaser or any of such purchaser's affiliates, and any other persons whose beneficial ownership of common stock would or could be aggregated with such purchaser's purchaser's for purposes of Section 13(d) or Section 16 of the Exchange Act) would exceed 9.99% of the number of shares of common stock outstanding immediately after giving effect to the exercise, as such percentage ownership is determined in accordance with the terms of such warrant, which percentage may be increased or decreased at such purchaser's election upon 61 days' notice to us subject to the terms of such warrants, provided that such percentage may in no event exceed 19.99%. We refer to such percentage limitations as the September 2022 Offering Beneficial Ownership Limitations. The shares of common stock and the pre-funded

warrants were issued pursuant to a prospectus supplement dated September 22, 2022 to the Prior Shelf Registration Statement. A purchaser may not exercise, and subsequently resell the underlying shares of common stock of, any portion of the pre-funded warrants to the extent such exercise would result in such purchaser exceeding the applicable September 2022 Offering Beneficial Ownership Limitation. The purchasers will be able to resell all, some or none of the shares of common stock registered pursuant to the Prior Shelf Registration Statement at any time or in their discretion, subject to the September 2022 Offering Beneficial Ownership Limitations. As of March 16, 2023 March 20, 2024, all of the pre-funded warrants that we issued to purchasers and sold in the September 2022 Offering to purchase 13,270,983 shares of common stock remained outstanding.

Sales of substantial amounts of shares of our common stock or other securities by our stockholders, by us under the Shelf Registration Statement, whether pursuant to the 2023 ATM Sales Agreement or otherwise, by Lincoln Park Capital Fund, LLC, or Lincoln Park, pursuant to the Form S-1, by the private placement investors pursuant to the Initial Private Placement Form S-3, the Second Private Placement Form S-3 or the Third Private Placement Form S-3 or through any other means could also lower the market price of our common stock, make it more difficult for you to sell your shares at a price that you desire and impair our ability to raise capital through the sale of equity or equity-related securities.

The number of shares of common stock underlying our outstanding warrants is significant in relation to our currently outstanding common stock, which could have a negative effect on the market price of our common stock and make it more difficult for us to raise funds through future equity offerings. In addition, in connection with any merger, consolidation or sale of all or substantially all of our assets, holders of our outstanding warrants would be entitled to receive consideration in excess of their reported beneficial ownership of our common stock and this could adversely impact the consideration our other stockholders would receive.

As part of our October 2021 Private Placements, private placements, we issued to the Initial Private Placement Investor warrants to purchase an aggregate of 14,598,540 shares of our common stock at an exercise price of $1.37 per share, and pre-funded warrants to purchase up to an aggregate of 4,926,069 shares of our common stock at an exercise price of $0.001 per share, which as of February 10, 2022 have had been exercised in full. Of the common stock warrants issued to the Initial Private Placement Investor at an exercise price of $1.37 per share, warrants to purchase an aggregate of 7,299,270 shares will expire on April 5, 2025 and warrants to purchase an aggregate of 7,299,270 shares will expire on October 5, 2028. In addition, we issued to NEA warrants to purchase an aggregate of 3,703,704 shares of our common stock at an exercise price of $1.37 per share. Of the common stock warrants issued to NEA, warrants to purchase an aggregate of 1,851,852 shares of our common stock will expire on April 18, 2025 and warrants to purchase an aggregate of 1,851,852 shares of our common stock will expire on October 18, 2028. We issued pre-funded warrants to purchase up to an aggregate of 24,379,673 shares of our common stock to the purchasers in the April 2022 Private Placement. Placement, of which pre-funded warrants to purchase 17,282,760 shares of common stock remained outstanding as of March 20, 2024. Finally, we issued pre-funded warrants to purchase up to an aggregate of 14,247,330 shares of our common stock at an exercise price of $0.001 per share to certain

purchasers in the September 2022 Offering. Offering, of which pre-funded warrants to purchase 13,270,983 shares of common stock remained outstanding as of March 20, 2024.

As discussed above, the common stock warrants issued to the Initial Private Placement Investor are subject to the Initial Investor Beneficial Ownership Limitations, the pre-funded warrants issued to the purchasers in the April 2022 Private Placement are subject to the 2022 Private Placement Beneficial Ownership Limitations and the pre-funded warrants issued to certain purchasers in the September 2022 Offering are subject to the September 2022 Offering Beneficial Ownership Limitations. Although the Initial Private Placement Investor's warrants are subject to the Initial Investor Beneficial Ownership Limitations, the pre-funded warrants issued to the purchasers in the April 2022 Private Placement are subject to the 2022 Private Placement Beneficial Ownership Limitations and the pre-funded warrants issued to the purchasers in the September 2022 Offering are subject to the September 2022 Offering Beneficial Ownership Limitations, upon exercise in full of the warrants, the shares issuable upon exercise would represent a significant portion of our outstanding common stock. As a result, the Initial Private Placement Investor, NEA and the other purchasers in the April 2022 Private Placement and the September 2022 Offering may be able to exert substantial influence over our business. The concentration of voting power resulting from the exercise of the warrants could delay, defer or prevent a change of control, entrench our management and our board of directors or delay or prevent a merger, consolidation, takeover or other business combination involving us on terms that other stockholders may desire. In addition, conflicts of interest could arise in the future between us, on the one hand, and the Initial Private Placement Investor, NEA, the purchasers in the April 2022 Private Placement and/or the purchasers in the September 2022 Offering on the other hand, concerning potential competitive business activities, business opportunities, the issuance of additional securities and other matters. In addition, sales of these shares could cause the market price of our common stock to decline significantly.

Furthermore, in the event of a sale of our company, whether by merger, sale of all or substantially all of our assets or otherwise, the holders of warrants would be entitled to receive, with respect to each share of common stock issuable upon exercise of the warrants then held by them and, and in the case of the Initial Private Placement Investor, without regard to the Beneficial Ownership Limitations, the same amount and kind of securities, cash or property as they would have been entitled to receive if such securities had been converted into or exercised for shares of our common stock immediately prior to such sale of our company. Although the Initial Private Placement Investor's beneficial ownership of our common stock

is reported as 9.99% as a result of the application of the Beneficial Ownership Limitations, in the event of a sale of our company, the Initial Private Placement Investor would receive sale consideration without regard to the Beneficial Ownership Limitations. In such a sale, the Initial Private Placement Investor would be entitled to receive a significantly larger portion of

the total proceeds distributable to the holders of our securities than is represented by its reported beneficial ownership of our common stock. In addition, pursuant to the terms of the common stock warrants issued to both the Initial Private Placement Investor and NEA in our October 2021 Private Placements, in specified circumstances upon a fundamental transaction by us, such warrant holders may have the right to require us to repurchase their common stock warrants at their fair value using a Black Scholes option pricing formula. As a result, in the event of a sale of our company, the Initial Private Placement Investor and NEA may be entitled to receive a significantly larger portion of the total proceeds distributable to our stockholders than they would if they exercised the warrants immediately prior to the transaction, and our stockholders could receive significantly less than they otherwise would in such a transaction.

Given the amount and terms of these warrants, we may find it more difficult to raise additional equity capital on favorable terms or at all while these warrants are outstanding.

Ownership of our common stock is concentrated among our executive officers and directors and their affiliates, who have significant influence over our business, which may prevent new investors from influencing significant corporate decisions.

Our executive officers and directors and their respective affiliates, beneficially own, in the aggregate, shares representing approximately 37.5% 24.9% of our common stock as of March 16, 2023 March 20, 2024. As a result, our executive officers and directors and their affiliates acting together may be able to significantly influence all matters submitted to our stockholders for approval, as well as our management and affairs. This concentration of ownership control may:

- delay, defer or prevent a change in control;
- entrench our management or the board of directors; or
- impede a merger, consolidation, takeover, sale, other business combination or other significant corporate transaction involving us that other stockholders may desire.

Some of these persons or entities may have interests different than yours. For example, certain of these stockholders may have purchased their shares at prices substantially below the prices you paid for your shares or may have held their shares for a longer period, and they may be more interested in selling our company to an acquirer or they may want us to pursue strategies that deviate from your interests.

We do not anticipate paying any cash dividends on our capital stock in the foreseeable future. Accordingly, stockholders must rely on appreciation in the price of our common stock, if any, for any return on their

investment.

We have never declared or paid cash dividends on our capital stock and we do not intend to do so in the foreseeable future. We currently plan to retain all of our future earnings, if any, to finance the operation, development and growth of our product pipeline and business. In addition, the terms of the SVB Term Loan preclude us from paying dividends and any future debt or credit agreements may also preclude us from paying dividends. As a result, future appreciation, if any, in the market value of our common stock will be your sole source of gain for the foreseeable future. There is no guarantee that our common stock will appreciate or even maintain the price at which our holders have purchased it.

We are an "emerging growth company" and a "smaller reporting company" and the reduced disclosure requirements applicable to us may make our common stock less attractive to investors.

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and may remain an emerging growth company for up to five years. years, or until December 31, 2024. For so long as we remain an emerging growth company, we are permitted and plan to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, as amended, or SOX Section 404, not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements, reduced disclosure obligations regarding executive compensation in our periodic reports, proxy statements and registration statements and not being required to hold a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved. Even after we no longer qualify as an emerging growth company, we may still qualify as a "smaller reporting company," which would allow us to take advantage of many of the same exemptions from disclosure requirements, including not being required to comply with the auditor attestation requirements of SOX Section 404 and reduced disclosure obligations regarding executive compensation. If some investors find our common stock less attractive as a result of our reliance on these exemptions, the trading market for our common stock may be less active and our stock price may be more volatile.

We incur increased costs as a result of operating as a public company and our management is required to devote substantial time to compliance initiatives and corporate governance practices.

As a public company and particularly after we are no longer an "emerging growth company" or a "smaller reporting company," we incur and will continue to incur, significant legal, accounting, investor relations and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of the Nasdaq Stock Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. We may need to hire additional accounting, finance and other personnel in connection with our efforts to comply with the requirements of being a public company and our management

and other personnel devote a substantial amount of time in complying with these requirements, which could negatively impact our financial results. Current and changing laws, rules and regulations relating to corporate governance and public disclosure may increase our legal and financial compliance costs and make some activities more time-consuming and costly. For example, the rules and regulations applicable to us as a public company have made it and we expect that they may continue to make it, more difficult and more expensive for us to obtain director and officer liability insurance, which could make it more difficult for us to attract and retain qualified members of our board of directors. We are evaluating these rules and regulations and cannot currently predict or estimate the additional costs we may incur or the timing of such costs. In addition, these laws, rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices. We have invested in and intend to continue to invest in, resources to comply with evolving laws, rules and regulations and this investment may result in increased general and administrative expenses and a diversion of management's time and attention from revenue generating activities to compliance activities. If, notwithstanding our efforts to comply with new laws, rules and regulations, we fail to comply, regulatory authorities may initiate legal proceedings against us and our business may be harmed.

If we fail to maintain proper and effective internal controls, our ability to produce accurate financial statements on a timely basis could be impaired.

We are subject to the reporting requirements of the Securities Exchange Act of 1934, or the Exchange Act, the Sarbanes-Oxley Act of 2002 and the rules and regulations of the Nasdaq Stock Market. The Sarbanes-Oxley Act of 2002 requires, among other things, that we maintain effective disclosure controls and procedures and internal control over financial reporting. Pursuant to SOX Section 404, we are required to furnish annual reports by our management on our

internal control over financial reporting. However, while we remain an emerging growth company or a smaller reporting company with less than $100 million in annual revenue, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with SOX Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement

process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude that our internal control over financial reporting is effective. If we are unable to comply with the requirements of SOX Section 404 in a timely manner or if we are unable to maintain proper and effective internal controls, we may not be able to produce timely and accurate financial statements. If that were to happen, the trading price of our common stock could decline and we could be subject to sanctions or investigations by the Nasdaq Stock Market, the SEC or other regulatory authorities.

We might not be able to utilize a significant portion of our net operating loss carryforwards and research and development tax credit carryforwards.

As of December 31, 2022 December 31, 2023, we had federal and state net operating loss carryforwards of $178.4 million $186.9 million and federal research and development tax credit carryforwards of $5.4 million $6.2 million, which if not utilized generally will begin to expire in 2031 and 2032, respectively. These net operating loss and research and development tax credit carryforwards could expire unused and be unavailable to offset future income tax liabilities. In general, under Section Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or the IRC, and corresponding provisions of state law, a corporation that undergoes an "ownership change," generally defined as a greater than 50 percentage point change (by value) in its equity ownership by certain stockholders over a three year period, is subject to limitations on its ability to utilize its pre-change net operating losses loss and research and development tax credit carryforwards to offset future taxable income. We previously completed a Section 382 analysis, and due to multiple historical ownership changes, all of our net operating loss carryforwards as of December 31, 2022, and research and development tax credits are were subject to limitation. If a further ownership change occurs, our ability to use our tax attributes might be further

limited. In addition to potential Section 382 limitations, there are other factors that might limit the availability of our tax attributes. For example, we have not conducted a detailed research and development tax credit analysis to document whether our historical business activities qualify to support our research and development credit carryforwards. A detailed study could result in adjustment to our research and development credit carryforwards.

There is also a risk that due to regulatory changes, such as suspensions on the use of net operating losses or other unforeseen reasons, our existing net operating losses could expire or otherwise become unavailable to offset future income tax liabilities. As described below in "Changes in tax laws or in their implementation or interpretation may adversely affect our business and financial condition," the Tax Cuts and Jobs Act, or the Tax Act, as amended by the Coronavirus Aid, Relief and Economic Security Act, or CARES Act, includes changes to U.S. federal tax rates and the rules governing net operating loss carryforwards that may significantly impact our ability to utilize our net operating losses to offset taxable income in the future. In addition, state net operating losses generated in one state cannot be used to offset income generated in another state. For these reasons, even if we attain profitability, we may be unable to use a material portion of our net operating losses and other tax attributes.

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

Recent changes in tax law may adversely affect our business or financial condition. On December 22, 2017, the U.S. government enacted the Tax Act, which significantly reformed the IRC. The Tax Act, among other things, as amended by the CARES Act, contained significant changes to corporate taxation, including a reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, the limitation of the tax deduction for net interest expense to 30% of adjusted taxable income (except for certain small businesses), and the limitation of the deduction for net operating losses arising in taxable years beginning after December 31, 2017 to 80% of current year taxable income and elimination of net operating loss carrybacks for such losses arising in taxable years ending after December 31, 2017 (though any such NOLs may be carried forward indefinitely), . In addition, beginning in 2022, the imposition Tax Act eliminated the option to deduct research and development expenditures currently and generally requires corporations to capitalize and amortize them over five years or 15 years in the case of a one-time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, the elimination of U.S. tax on expenditures attributable to foreign earnings (subject to certain important exceptions), the allowance of immediate deductions for certain new investments instead of deductions for depreciation expense over time and the modification or repeal of many business deductions and credits.research.

As In addition to the CARES Act, as part of Congress's response to the COVID-19 pandemic, the Families First Coronavirus Response Act, or FFCR Act, economic relief legislation was enacted on March 18, 2020 in 2020 and the CARES Act was enacted on March 27, 2020. Both contain numerous 2021 containing tax provisions. In particular, the CARES Act retroactively and temporarily (for taxable years beginning before January 1, 2021) suspends application The IRA was also signed into law in August 2022. The IRA introduced new tax provisions, including a 1% excise tax imposed on certain stock repurchases by publicly traded companies. The 1% excise tax generally applies to any acquisition of stock by a publicly traded company (or certain of its affiliates) from a stockholder of the 80%-of-income limitation on the use of net operating losses, which was enacted as part company in exchange for money or other property (other than stock of the Tax Act. It also provides company

---

itself), subject to a de minimis exception. Thus, the excise tax could apply to certain transactions that net operating losses arising in any taxable year beginning after December 31, 2017 and before January 1, 2021, are generally eligible to be carried back up to five years. The CARES Act also temporarily (for taxable years beginning in 2019 or 2020) relaxes the limitation of the tax deductibility for net interest expense by increasing the limitation from 30 to 50% of adjusted taxable income. not traditional stock repurchases.

Regulatory guidance under the Tax Act, the FFCR Act IRA, and the CARES Act such additional legislation is and continues to be forthcoming and such guidance could ultimately increase or lessen impact of these laws on our business and financial condition. It is also likely that Congress will enact additional legislation in connection with the COVID-19 pandemic, some of which could have an impact on us. In addition, it is uncertain if and to what extent various states will conform to the Tax Act, the FFCR Act or the CARES Act. IRA, and such additional legislation.

Provisions in our organizational documents and under Delaware law may prevent or frustrate attempts by our stockholders to change our management or hinder efforts to acquire a controlling interest in us.

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

- establish a classified board of directors such that all members of the board are not elected at one time;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from the board;

- establish advance notice requirements for nominations for election to the board of directors or for proposing matters tha can be acted on at stockholder meetings;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call a special meeting of stockholders;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a "poison pill" that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitio that have not been approved by our board of directors; and
- require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to ame or repeal certain provisions of our certificate of incorporation or bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the General Corporation Law of the State of Delaware, which prohibits an "interested stockholder," which is either a person who owns at least 15% of our outstanding voting stock or an affiliate or associate who owned at least 15% of our outstanding voting stock at any time within the prior three years, from engaging in a business combination with us for a period of three years after the date of the transaction in which the person became an "interested stockholder" unless the business combination is approved in a prescribed manner. This could discourage, delay or prevent someone from acquiring us or merging with us, whether or not it is desired by or beneficial to, our stockholders. This could also have the effect of discouraging others from making tender offers for our common stock, including transactions that may be in your best

interests. These provisions may also prevent changes in our management or limit the price that investors are willing to pay for our stock.

Our certificate of incorporation provides that the Court of Chancery of the State of Delaware will be the exclusive forum for substantially all disputes between us and our stockholders and that the federal district courts of the U.S. are the sole and exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act. These choice of forum provisions could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our certificate of incorporation provides that the Court of Chancery of the State of Delaware (or, if the Court of Chancery of the State of Delaware does not have jurisdiction, the federal district court for the District of Delaware) shall, to the fullest extent permitted by law, be the sole and exclusive forum for (1) any derivative action or proceeding brought on behalf of our company, (2) any action asserting a claim of breach of fiduciary duty owed by any director, officer, other employee or stockholder of our company to us or our stockholders, (3) any action asserting a claim arising pursuant to any provision of the Delaware General Corporation Law or as to which the Delaware General Corporation Law confers jurisdiction on the Court of Chancery or (4) any action asserting a claim arising pursuant to any provision of our certificate of incorporation or bylaws or governed by the internal affairs doctrine. Our certificate of incorporation further provides

---

that, unless we consent in writing to the selection of an alternative forum, the federal district courts of the U.S. shall, to the fullest extent permitted by law, be the sole and exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act. Neither of these choice of forum provisions would affect suits brought to enforce any liability or duty created by the Exchange Act or the rules and regulations thereunder, jurisdiction over which is exclusively vested by statute in the U.S. federal courts or any other claim for which U.S. federal courts have exclusive jurisdiction.

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

Risks Related to Our Business Operations

We face risks related to health epidemics and other widespread outbreaks of contagious disease, including the COVID-19 pandemic, which has delayed our ability to complete our ongoing clinical trials, disrupted our business operations and may further delay our clinical trials, interrupt our supply chain, disrupt regulatory activities, or have other adverse effects on our business and operations. In addition, the COVID-19 pandemic has caused substantial disruption in the financial markets and economies worldwide, which could result in adverse effects on our business and operations.

Significant outbreaks of contagious diseases, such as COVID-19, and other adverse public health developments, could have a material impact on our business operations and operating results.

The COVID-19 pandemic and government measures taken in response thereto have also had a significant impact, both direct and indirect, on segments of the global economy and have interrupted our clinical trial activities, disrupted our business operations and have the potential to interrupt our supply chain. We have experienced restrictions and delays at our existing clinical sites. For example, the clinical sites in our Phase 2 CANAL trial for chronic cough in adults with IPF experienced delays in the enrollment and treatment of subjects in the trial due to the vulnerability of IPF patients to COVID-19 and as a result, we amended the protocol for the trial to reduce the number of in-person subject visits and procedures. Any trials we may conduct in the future for the treatment of chronic cough in adults with IPF or other chronic cough conditions could be delayed or negatively impacted by the COVID-19 pandemic or other outbreaks of infectious diseases due to the vulnerability of this patient population to respiratory illness. In addition, in our Phase 2b/3 PRISM trial, new subject screening and most enrollment was temporarily halted in March 2020 due to the COVID-19 pandemic. After resuming screening and enrollment, multiple sites in the Phase 2b/3 PRISM trial required some remote monitoring of subject data. We also experienced slower recruitment activities in the Phase 2b/3 PRISM trial worldwide through the latter part of 2020 and the beginning of 2021 due to the resurgence of COVID-19. Although the Phase 2 CANAL trial and the Phase 2b/3 PRISM trial open-label extension have concluded, the COVID-19 pandemic and other outbreaks of infectious disease could still adversely affect our ability to retain subjects, principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19 and other infectious diseases and may result in further disruptions to our clinical trials in the future due to prioritization of hospital and medical resources toward the pandemic or future outbreaks, restrictions on travel of patients and healthcare providers, or potential inability of subjects to comply with clinical trial protocols if quarantines or travel restrictions impede subject movement or interrupt healthcare services. The response to the COVID-19 pandemic may also redirect resources of regulators in a way that could adversely impact our ability to progress regulatory approvals and we may face impediments to regulatory meetings and approvals relating to our clinical trials due to measures intended to limit in-person interactions.

The COVID-19 pandemic may also affect employees of third-party contract research organizations located in affected geographies that we rely upon to carry out our clinical trials. The spread of COVID-19 or another infectious disease, could also negatively affect the operations at our third-party suppliers, which could result in delays or disruptions in the supply of drug product used in our clinical trials.

We cannot presently predict the scope and severity of the disruptions we may experience or continue to experience as a result of the COVID-19 pandemic or other outbreaks of infectious disease. If we or any of the third parties with whom we engage experience business disruptions, our ability to conduct our business in the manner and on the timelines presently planned could be materially and negatively affected. Additionally, the pandemic has already caused significant disruptions in the financial markets and may continue to cause such disruptions, which could impact our ability to raise additional funds and has also impacted, and may continue to impact, the volatility of our stock price and trading in our stock.

While the current trajectory of the COVID-19 pandemic is uncertain, in the future we may continue to experience adverse impacts on our clinical trial activities, business operations, financial condition, and prospects as a result of the future evolution of the virus, among other factors.

Item 1B. Unresolved Staff Comments.

Not applicable.

Item 1C. Cybersecurity.

We have certain processes for assessing, identifying and managing cybersecurity risks, which are built into our overall risk management program and information technology function and are designed to help protect our information assets and operations from cyber threats, protect employee and patient information from unauthorized access or attack, as well as secure our networks and systems. Such processes include physical, procedural and technical safeguards, and routine review of our operations to identify risks and enhance our practices. We engage certain external parties, including consultants and computer security firms, to enhance our cybersecurity oversight. We consider the internal risk oversight programs of third-party service providers when engaging them in order to help protect us from any related vulnerabilities.

Our board of directors does not believe that there are currently any known risks from cybersecurity threats that are reasonably likely to materially affect us or our business strategy, results of operations or financial condition.

The audit committee of our board of directors provides direct oversight over cybersecurity risk and provides updates to the board of directors regarding such oversight. The audit committee receives periodic updates from management regarding cybersecurity matters and is notified between such updates regarding significant new cybersecurity threats or incidents.

We have also established a Cybersecurity Committee that meets on a quarterly basis to review and agree on actions to address cybersecurity risks. The Cybersecurity Committee is led by our chief information officer, or CIO, who is a part-time consultant and includes our chief executive officer and chief financial officer. Our CIO, who reports to our chief financial officer, is responsible for the strategic leadership of our cybersecurity programs, identification of cybersecurity risks and the mitigation plans that address these risks. With over 25 years of experience in information technology, the CIO works alongside individuals across other functions, such as clinical operations, legal and quality compliance, to establish and implement our cybersecurity strategy. Our CIO has a bachelor’s degree in Technology and an M.B.A. along with over 10 years of experience in information technology in the life sciences industry.

In an effort to deter and detect cyber threats, we annually provide all employees, including part-time and temporary employees, with a data protection, cybersecurity training and compliance program, which covers timely and relevant topics, including social engineering, phishing, password protection, confidential data protection, and asset use, and educates employees on the importance of reporting all incidents immediately. We conduct frequent phishing simulations requiring employees to identify and report simulated phishing emails. We also use technology-based tools to mitigate cybersecurity risks and to bolster our employee-based cybersecurity programs.

Item 2. Properties.

Our headquarters is currently located in New Haven, Connecticut, and consists of approximately 12,500 square feet of leased office space under a lease that expires in February 2028 and under which we have an option to extend the lease by a five-year term. We believe that our existing facilities are adequate for our current needs; however, we may require additional space and facilities as our business expands.

Item 3. Legal Proceedings.

We are not subject to any material legal proceedings.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

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

Market Information

Our common stock is listed on the Nasdaq Stock Market LLC under the symbol "TRVI."

Stockholders

As of March 16, 2023 March 20, 2024, there were approximately 20 holders of record of our common stock. 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.

Dividend Policy

We have never declared or paid cash dividends on our common stock and we do not intend to pay any cash dividends in the foreseeable future. We currently intend to retain all available funds and any future earnings to finance the operation, development and growth of our business. In addition, the terms of the SVB Term Loan preclude us from paying dividends and the terms of any future debt or other financing that we may obtain may also preclude us from declaring or paying dividends on our common stock. Any future determination to declare and pay dividends will be made at the discretion of our board of directors and will depend on then-existing conditions, including our results of operations, financial condition, contractual restrictions, capital requirements, business prospects and other factors our board of directors may deem relevant.

Securities Authorized for Issuance Under Equity Compensation Plan

The information concerning our equity compensation plan is incorporated by reference from the information in our Proxy Statement for our 2023 2024 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

Item 6. [Reserved]

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

The following discussion and analysis of our financial condition and results of operations should be read in conjunction with our consolidated financial statements Consolidated Financial Statements and related notes appearing elsewhere in this Annual Report on Form 10-K. Some of the statements contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business, constitute forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. The words "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "might," "plan," "potential," "predict," "project," "should," "target," "would," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We have based these forward-looking statements on our current expectations and projections about future events. The following information and any forward-looking statements should be considered in light of factors discussed elsewhere in this Annual Report on Form 10-K, particularly including those risks identified in Part I-Item 1A "Risk Factors" and our other filings with the SEC.

Our actual results and timing of certain events may differ materially from the results discussed, projected, anticipated, or indicated in any forward-looking statements. We caution you that forward-looking statements are not guarantees of future performance and that our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate may differ materially from the forward-looking statements contained in this Annual Report on Form 10-K. Statements made herein are as of the date of the filing of this Annual Report on Form 10-K with the SEC and should not be relied upon as of any subsequent date. Even if our results of operations, financial condition and liquidity, and the development of the industry in which we operate are consistent with the forward-looking statements contained in this Annual Report on Form 10-K, they may not be predictive of results or developments in future periods. We disclaim any obligation, except as specifically required by law and the rules of the SEC, to publicly update or revise any such statements

to reflect any change in our expectations or in events, conditions or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements.

We caution readers not to place undue reliance on any forward-looking statements made by us, which speak only as of the date they are made.

Overview

We are a clinical-stage biopharmaceutical company focused on the development and commercialization of the investigational therapy Haduvio (oral nalbuphine ER) for the treatment of chronic cough in adults with idiopathic pulmonary fibrosis, or IPF, and other refractory chronic cough, indications, and for the treatment of prurigo nodularis.or RCC.

Chronic Cough. IPF Program. In September 2022, we announced positive data from the full set of patients in our Phase 2 clinical trial of Haduvio for the treatment of chronic cough in adults with IPF, which we refer to as the Phase 2 CANAL trial. The Phase 2 CANAL trial was a randomized, double-blind, placebo controlled, two-treatment, two-period, crossover study that was designed to

---

evaluate the efficacy, safety, tolerability and dosing of Haduvio for chronic cough in adults with IPF that we conducted at multiple sites in the United Kingdom. In total, we enrolled 38 subjects 42 patients in the study. study received Haduvio. In the full subject data set, Phase 2 CANAL trial, Haduvio demonstrated statistically significant results for the primary efficacy endpoint of daytime cough frequency reduction ($p<0.0001$) and for key secondary endpoints on patient and clinician reported outcomes. The safety results of the trial were generally consistent with the known safety profile of Haduvio from previous trials in other patient populations.

In December 2023, we initiated our Phase 2b CORAL clinical trial, which is a dose-ranging study evaluating the efficacy, safety and tolerability of Haduvio for chronic cough in IPF. This trial is expected to be conducted at multiple sites in up to 11 countries and uses a randomized, double-blind, placebo-controlled, parallel-arm design, which evaluates three doses of Haduvio over six weeks as compared to placebo. The primary efficacy endpoint for the trial is the relative change in 24-hour cough frequency at the end of week six versus baseline for Haduvio compared to placebo, as measured via an objective cough monitor. We expect the trial to enroll approximately 160 patients. The protocol for the Phase 2b CORAL clinical trial provides for a sample size re-estimation, or SSRE, analysis once approximately 50% of the patients in the trial are evaluable for the primary endpoint. The SSRE is expected to occur in the second half of 2024, and topline data from

the full trial are expected to be available in the first half of 2025 assuming there are no adjustments made to the sample size.

We are expect to have an active investigational new drug application for our planned Phase 1b clinical trial to evaluate the effect of Haduvio on respiratory physiology in discussions patients with IPF of varying disease severity in the first half of 2024. We expect the objective for this clinical trial will be to further characterize the safety of Haduvio in this specific patient population. Subject to agreement with the U.S. Food and Drug Administration, or FDA, and other regulatory international regulatory authorities, regarding the design of the next clinical trials of Haduvio for the treatment of chronic cough in adult patients with IPF. We expect the objectives for the next trials will be to determine the dose response and select the dose for the next study as well as to further characterize the safety in this specific patient population. Subject to agreement with the FDA, and other international regulatory authorities, we intend to initiate these trials this trial in the second first half of 2023. We will need to submit an IND for Haduvio before proceeding with our planned trials for chronic cough in adults with IPF at sites in the United States.2024.

*RCC Program.*We are also plan to develop developing Haduvio for additional chronic cough indications, the treatment of RCC. In November 2023, we initiated our Phase 2a clinical trial of Haduvio for RCC, which we expect will commence initially with refer to as the Phase 2a RIVER trial. The Phase 2a RIVER trial is a Phase 2 clinical trial randomized, double-blind, placebo-controlled, two-treatment, two-period, crossover study that is designed to evaluate the efficacy, safety, tolerability and dosing of Haduvio for the treatment of refractory chronic cough, which we expect to initiate in the third quarter of 2023 RCC. We are conducting this trial at multiple sites in the U.K. United Kingdom and Canada. The trial was designed to enroll approximately 60 adult patients. The primary endpoint of the study is a mean change in 24-hour cough frequency using an objective cough monitor in the overall population. Patients are randomized with a 1:1 stratification between those with 10-19 coughs/hour (moderate 24-hour cough frequency) and those with at least 20 coughs/hour (high 24-hour cough frequency). The study will also explore secondary endpoints, including patient reported outcome measures for cough frequency and severity. We expect to report topline efficacy and safety data in the second half of 2024.

Human Abuse Potential. We initiated a human abuse potential, or HAP, study in the fourth quarter of 2022 to compare the abuse potential of oral nalbuphine to intravenous, or IV, butorphanol. The injectable version of nalbuphine is currently unscheduled in the U.S. by the Drug Enforcement Agency. The study follows a randomized, double-blind, active and placebo-controlled five-way crossover design. The study is being conducted in two parts. The first part of the study characterized various IV butorphanol doses in order to select a dose to be studied. The second part of the study is designed to utilize the selected dose and compare oral nalbuphine relative to IV butorphanol using the study metrics. We have completed the first part of the study. The FDA requested that we submit the data from the first part of the study in support of our IV butorphanol dose selection for their review and comment prior to commencing the second part of the study. We submitted this data to the FDA and the FDA agreed with the selected dose for IV butorphanol. We initiated dosing in the second part of the study in January 2024, and, as of March 11, 2024, the study was over 50% enrolled. We expect to report topline data from the study in the second half of 2024.

Prurigo Nodularis Program. .We also have a development program for the use of Haduvio for the treatment of prurigo nodularis. In June 2022, we reported positive results in our Phase 2b/3 clinical trial of Haduvio in patients with prurigo nodularis, which we refer to as the Phase 2b/3 PRISM trial. The Phase 2b/3 PRISM trial was a randomized, double-blind,

placebo controlled, two-arm treatment study that was designed to evaluate the safety and efficacy of Haduvio in patients with prurigo nodularis in the United States and Europe. In total we enrolled 353 patients in the study. In the Phase 2b/3 PRISM trial, Haduvio demonstrated statistically significant results on the primary and all three key secondary endpoints. The safety results of the trial were generally consistent with the known safety profile of Haduvio from previous trials.trials in other patient populations.

We are analyzing In October 2023, we reported the preliminary analysis of the 52-week data from the open-label extension portion of the Phase 2b/3 PRISM trial. Following the completion of the initial 14-week portion of the trial, patients were eligible to enroll into an additional 38-week open-label extension period during which we all participants received Haduvio 162mg twice a day (BID). Post hoc analyses demonstrated continued reduction in mean Worst Itch Numerical Rating Scale for those

---

participants who remained on Haduvio through 52 weeks. 151 patients completed the open-label extension portion of the trial, adding to the safety database for Haduvio. The safety data were generally consistent with the safety profile of Haduvio observed in the first quarter 14-week portion of 2023. the Phase 2b/3 PRISM trial and previous trials of Haduvio. Adverse events reported with a frequency greater than five percent in the 38-week open-label period included nausea, dizziness, vomiting, fatigue, and somnolence. Study discontinuation due to treatment-related adverse events occurred in 13% of patients during the 38-week open-label period, and serious adverse events were reported for 13 patients, although only two of these events were considered potentially treatment related.

We expect that we will need to conduct an additional Phase 3 clinical trial to support the submission of a new drug application, or NDA, to the FDA, a marketing authorization application, or MAA, to the European Medicines Agency or EMA, and an MAA to the Medicines and Healthcare Products Regulatory Agency in the United Kingdom or MHRA, for Haduvio for the treatment of prurigo nodularis, and plan to request an end of Phase 2 meeting with the FDA in 2023. FDA. Following discussions with the FDA and other regulatory authorities, we plan to determine next steps with respect to our prurigo nodularis program, including with respect to the conduct of any future Phase 3 clinical trial. We are exploring entering may seek to enter into a strategic collaboration for the continued development of this program.

Human Abuse Liability Study. We initiated a human abuse liability study in the fourth quarter of 2022 to compare the abuse potential of oral nalbuphine to butorphanol. The injectable version of nalbuphine is currently unscheduled in the U.S. by the Drug Enforcement Agency. The study is a randomized, double-blind, active and placebo-controlled 5-way crossover design. The study will be conducted in two parts, with the first part characterizing various butorphanol doses. One butorphanol dose will be selected to be studied in the second part of the protocol to determine the abuse potential of oral

nalbuphine relative to butorphanol. We are currently completing part one of the study and we expect top-line data from this trial by the end of 2023.

Since commencing operations in 2011, we have devoted substantially all of our efforts and financial resources to the clinical development of Haduvio. We have not generated any revenue from product sales and, as a result, we have never been profitable and have incurred net losses in each year since commencement of our operations. As of December 31, 2022 December 31, 2023, we had an accumulated deficit of $210.1 million $239.1 million, primarily as a result of research and development and general and administrative expenses. We do not expect to generate product revenue unless and until we obtain marketing approval for and commercialize Haduvio for the treatment of chronic cough in adults with IPF or other chronic cough indications and RCC or for the treatment of prurigo nodularis and we can provide no assurance that we will ever generate significant revenue or profits.

In May 2019, we issued and sold 5,500,000 shares of common stock in our initial public offering, or the IPO, and 1,500,000 shares of common stock in a concurrent private placement, in each case at an offering price of $10.00 per share, for combined net proceeds of $62.1 million after deducting aggregate underwriting discounts and commissions and private placement agent fees of $4.9 million and other offering expenses of $3.0 million. Upon the closing of the IPO, our preferred stock then outstanding converted into an aggregate of 10,381,234 shares of common stock.

In June 2020, we entered into a sales agreement with SVB Securities LLC (formerly SVB Leerink LLC), or SVB Securities, which we refer to as the ATM Sales Agreement, under which we may were able to issue and sell shares of common stock, from time to time, having an aggregate offering price of up to $12.0 million. In May 2022, we and SVB Securities amended the ATM Sales Agreement with SVB Securities to increase the maximum aggregate offering price of common stock that we may were able to issue and sell from time to time under the ATM Sales Agreement by $50.0 million, from $12.0 million to up to $62.0 million. Sales of common stock under the ATM Sales Agreement may were able to be made by any method that was deemed an “at-the-market” offering as defined in Rule 415(a)(4) under the Securities Act of 1933, as amended. We were not obligated to make any sales of our common stock under the ATM Sales Agreement. We began making sales pursuant to the ATM Sales Agreement in July 2020, and as of August 15, 2023, the date of termination of the ATM Sales Agreement, we had issued and sold an aggregate of 4,333,394 shares of common stock for gross proceeds of $12.7 million pursuant to the ATM Sales Agreement, before deducting estimated commissions and allocated fees of $1.0 million.

In June 2023, we filed with the SEC a universal shelf registration statement on Form S-3, or the Shelf Registration Statement, which allows us to offer and sell up to $200.0 million of common stock, preferred stock, debt securities, units and/or warrants from time to time pursuant to one or more offerings at prices and terms to be determined at the time of sale. The Shelf Registration Statement was filed to replace our prior universal shelf registration statement on Form S-3 and was declared effective on August 15, 2023. Further, in June 2023, we entered into a new sales agreement with Leerink Partners, LLC (formerly SVB Securities), or Leerink Partners, which we refer to as the 2023 ATM Sales Agreement, under which we may issue and sell shares of common stock, from time to time by any method that is deemed an “at-the-market” offering as defined in Rule 415(a)(4) under the Securities Act of 1933, as amended. We are not obligated to make any sales of our common stock under the 2023 ATM Sales Agreement. We began making filed a prospectus under the Shelf Registration Statement for the offer and sale of shares of our common stock having an aggregate offering price of up to

$75.0 million pursuant to the 2023 ATM Sales Agreement. In accordance with the terms of the 2023 ATM Sales Agreement, the ATM Sales Agreement terminated upon effectiveness of the Shelf Registration Statement, at which point we were no longer able to issue and sell shares of our common stock under the ATM Sales Agreement. As of December 31, 2023, we had not made any sales pursuant to the 2023 ATM Sales Agreement in July 2020, and as of December 31, 2022 we had issued and sold an aggregate of 3,583,394 shares of common stock for gross proceeds of $11.0 million, before deducting estimated commissions and allocated fees of $0.8 million.

In August 2020, we entered into a loan and security agreement, or the SVB Loan Agreement, with Silicon Valley Bank, or SVB, pursuant to which SVB provided a term loan, or the SVB Term Loan, to us in the original principal amount of $14.0 million. On the first business day of each month commencing on March 1, 2022, we were required to repay the SVB Term Loan in 24 consecutive installments of principal plus monthly payments of accrued interest. All outstanding principal and accrued and unpaid interest under the SVB Term Loan and all other outstanding obligations with respect to the SVB Term Loan are due and payable in full on February 1, 2024. The SVB Loan Agreement permits voluntary prepayment of all, but not less than all, of the SVB Term Loan, subject to a prepayment premium. In July 2021 and April 2022, we entered into amendments to the SVB Loan Agreement with SVB, which we refer to as the Loan Amendments, that modified the conditions under which we would be required to cash collateralize the outstanding amounts owed to them under the SVB Loan Agreement. For further discussion of the SVB Term Loan and the Loan Amendments, see “—Liquidity and Capital Resources”.

On October 5, 2021 and October 18, 2021, we issued and sold in two private placements, or the October 2021 Private Placements, in the aggregate (i) 4,225,053 shares of our common stock and accompanying warrants to purchase an aggregate of 8,450,106 shares of our common stock, and (ii) pre-funded warrants to purchase up to an aggregate of 4,926,069 shares of our common stock and accompanying warrants to purchase an aggregate of 9,852,138 shares of our common stock. Each share of our common stock and accompanying common stock warrants were sold together at a combined price of $1.62, and each pre-funded warrant and accompanying common stock warrants were sold together at a combined price of $1.619, for gross proceeds of approximately $14.8 million. Each pre-funded warrant had an exercise price of $0.001 per share, became exercisable immediately upon issuance and continued to be exercisable until exercised in full. Of the accompanying common stock warrants, we issued warrants to purchase an aggregate of 9,151,122 shares that

are to expire in April 2025 and warrants to purchase an aggregate of 9,151,122 shares that are to expire in October 2028. The accompanying common stock warrants have an exercise price of $1.37 per share and became exercisable immediately upon issuance. As of March 16, 2023 March 20, 2024, 1,851,852 of the warrants to purchase 1,851,852 shares of common stock that are to expire in April 2025 and 7,851,852 of the warrants to purchase 7,851,852 shares of common stock that are to expire in October 2028 remained outstanding.

On April 11, 2022, we issued and sold in a private placement, or the April 2022 Private Placement, (i) an aggregate of 4,580,526 shares of our common stock, and (ii) pre-funded warrants to purchase up to an aggregate of 24,379,673 shares of our common stock. Each share of our common stock was sold at a price of $1.90, and each pre-funded warrant was sold at a price of $1.899 per warrant share, for gross proceeds of approximately $55.0 million. Each pre-funded warrant has an exercise price of $0.001 per share, is exercisable immediately and will be exercisable until the pre-funded warrant is exercised in full. As of March 20, 2024, pre-funded warrants to purchase 17,282,760 shares of common stock that we issued and sold in the April 2022 Private Placement remained outstanding.

On September 27, 2022, we issued and sold 14,252,670 shares of our common stock and, in lieu of common stock to certain investors, pre-funded warrants to purchase 14,247,330 shares of common stock in a public offering, or the September 2022 Offering, at a public offering price of $1.93 per share of common stock and $1.929 per pre-funded warrant pursuant to an underwriting agreement, or the Underwriting Agreement, with SVB Securities, Stifel, Nicolaus & Company, Incorporated and Oppenheimer & Co. Inc., as representatives of the several underwriters, or the Underwriters. Each pre-funded warrant has an exercise price of $0.001 per share, is exercisable immediately and will be exercisable until the pre-funded warrant is exercised in full. Under the terms of the Underwriting Agreement, we agreed not to issue and sell additional shares until after November 21, 2022 except in certain circumstances, including the issuance and sale of additional shares pursuant to the Underwriting Agreement. Under the terms of the Underwriting Agreement, we granted the Underwriters an option, or the Option, exercisable for 30 days, to purchase up to an additional 4,275,000 shares of common stock, or the Additional Shares, at the public offering price of $1.93 per share. The Underwriters partially exercised the Option to purchase 1,600,428 Additional Shares, which shares were issued and sold on October 25, 2022. The September 2022 Offering, including the initial closing on September 27, 2022 and the Option closing on October 25, 2022, resulted in aggregate gross proceeds to us of approximately $58.1 million. As of March 20, 2024, pre-funded warrants to purchase 13,270,983 shares of common stock that we issued and sold in the September 2022 Offering remained outstanding.

On May 9, 2023, we paid the remaining amount due under the loan and security agreement, or the SVB Loan Agreement, that we originally entered into with Silicon Valley Bank, or SVB, in August 2020, resulting in the full extinguishment of the term loan thereunder, or the SVB Term Loan. The total payoff amount was $6.5 million, consisting of the remaining principal amount due of $5.2 million, the final payment fee of $1.2 million, and $0.1 million of accrued interest and prepayment premium. In August 2020, we entered into the SVB Loan Agreement with SVB, pursuant to which SVB provided the SVB Term Loan to us in the original principal amount of $14.0 million. On the first business day of each month commencing on March 1, 2022, we were required to repay the SVB Term Loan in 24 consecutive installments of principal plus monthly payments of accrued interest. All outstanding principal and accrued and unpaid interest under the SVB Term Loan and all other outstanding obligations with respect to the SVB Term Loan were due and payable in full on February 1,

2024. The SVB Loan Agreement permitted voluntary prepayment of all, but not less than all, of the SVB Term Loan, subject to a prepayment premium. For further discussion of the SVB Term Loan, see "—Liquidity and Capital Resources."

As of December 31, 2022 December 31, 2023, we had cash, cash equivalents and marketable securities of $120.5 million $83.0 million. We believe that our existing cash, cash equivalents and marketable securities will enable us to fund our operating expenses and capital expenditure requirements for at least 12 months from the date of issuance of the Consolidated Financial Statements included in this Annual Report on Form 10-K.

We expect to incur substantial expenditures in the foreseeable future as we advance Haduvio through clinical development, the regulatory approval process and, if approved, commercial launch activities. Specifically, in the near term, we expect to incur substantial expenses relating to the next trials we are conducting and plan to conduct for Haduvio including our Phase 2b CORAL clinical trial for the treatment of chronic cough in adults with IPF, our planned Phase 2 2a RIVER clinical trial of Haduvio for the treatment of refractory RCC, our planned Phase 1b respiratory physiology clinical trial for the treatment of chronic cough in IPF and the second part of our ongoing human abuse liability, or HAL, HAP study to determine compare the abuse potential of oral nalbuphine ER relative to IV butorphanol.

We will need substantial additional funding to support our continuing operations and pursue our growth strategy. Until such time as we can generate significant revenue from sales of Haduvio, if ever, we expect to finance our operations through the sale of equity, debt financings or other capital sources, including potential collaborations with other companies or other strategic transactions. Adequate funding may not be available to us on acceptable terms or at all. If we fail to raise capital or enter into such agreements as and when needed, we may have to significantly delay, scale back or discontinue the

development and commercialization of Haduvio for one or more indications or delay our efforts to expand our product pipeline.

Impacts of the COVID-19 Pandemic

The COVID-19 pandemic and government measures taken in response thereto have had a significant impact, both direct and indirect, on segments of the global economy and have interrupted our clinical trial activities, disrupted our business operations and have the potential to interrupt our supply chain. While the current trajectory of the COVID-19 pandemic is uncertain, in the future we may continue to experience adverse impacts on our clinical trial activities, business operations, financial condition, and prospects as a result of the future evolution of the virus, among other factors.86

We experienced restrictions and delays at our clinical sites for both our Phase 2b/3 PRISM and Phase 2 CANAL trials. The COVID-19 pandemic or other outbreaks of infectious disease may also adversely affect our ability to recruit and retain

principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19, and may result in further disruptions to our clinical trials due to prioritization of hospital and medical resources toward the pandemic, restrictions on travel of patients and healthcare providers, potential unwillingness of patients to enroll in trials at this time or the inability of patients to comply with clinical trial protocols if quarantines impede patient movement or interrupt healthcare services. The response to the COVID-19 pandemic may also redirect resources of regulators in a way that could adversely impact our ability to progress towards regulatory approvals and we may face impediments to regulatory meetings and approvals relating to our clinical trials due to measures intended to limit in-person interactions.

The COVID-19 pandemic may also affect employees of third-party contract research organizations that we rely upon to carry out our clinical trials. The spread of COVID-19 or another infectious disease could also negatively affect the operations at our third-party suppliers, which could result in delays or disruptions in the supply of drug product used in our clinical trials.

Components of Operating Results

Operating Expenses

Research and Development Expenses

For the periods presented, all of our research and development expenses consist of expenses incurred in connection with the development of Haduvio. These expenses include personnel-related costs, including stock-based compensation, consulting costs, contract manufacturing costs and fees paid to contract research organizations, or CROs, to conduct certain research and development activities on our behalf. We do not allocate all of our costs by each indication for which we are developing Haduvio, as a significant amount of our development activities broadly support all indications. In addition, several of our departments support our Haduvio drug candidate development program and we do not identify internal costs for each potential indication.

We expect our research and development expenses to increase over the next few years as we pursue our development program, pursue regulatory approval of Haduvio in the U.S., Europe and other jurisdictions outside the U.S. and prepare for a possible commercial launch of Haduvio. Predicting the timing or the cost to conduct our Haduvio development program and prepare for a possible commercial launch of Haduvio is difficult and delays may occur because of many factors including factors outside of our control. For example, if the FDA or other regulatory authorities were to require us to conduct clinical trials beyond those that we currently anticipate or if we experience significant delays in enrollment in any of our clinical trials, we could be required to expend significant additional financial resources and time on our development program. Furthermore, we are unable to predict when or if Haduvio will receive regulatory approval in the U.S. or elsewhere with any certainty.

General and Administrative Expenses

General and administrative expenses consist principally of personnel-related costs, including stock-based compensation for personnel in executive, finance, commercial and other administrative functions; professional fees for legal, consulting and accounting services; as well as rent and other general operating expenses not otherwise classified as research and development expenses.

We anticipate that our general and administrative expenses will increase as a result of increased personnel costs, including stock-based compensation and expanded infrastructure.

Other Income (Expense), Net

Change in Fair Value of Term Loan Derivative Liability

Before it was amended by the Third Amendment (as defined below), the SVB Loan Agreement provided that upon the occurrence of the Phase 3 Event, as described below, the interest rate on the SVB Term Loan would increase by 2.00%. This contingent interest rate increase represented a free-standing financial instrument. Accordingly, we accounted for the contingent interest rate increase as a derivative under Accounting Standards Codification, or ASC, 815, *Derivatives and Hedging*, and therefore, we recorded a term loan derivative liability for the contingent interest rate increase at its fair value.

We adjusted this liability to fair value at each reporting date it remained outstanding. We recognized changes in the fair value of this term loan derivative in our statements of comprehensive loss as a component of other income (expense), net. See below as discussed under "—Results of Operations—Operating Expenses—Other Income (Expense), Net."

Other Income (Expense), Net

For the year ended December 31, 2022, other income, net consisted of income related to an employee retention tax credit under the Coronavirus Aid, Relief, and Economic Security Act, or CARES Act. For the year ended December 31, 2021, other expense, net consisted of the value of the shares of our common stock that we issued to Lincoln Park Capital Fund, LLC, or Lincoln Park, as a commitment fee as consideration for Lincoln Park's commitment to purchase shares of our common stock under the common stock purchase agreement, or the LPC Purchase Agreement, we entered into in June 2021.

Interest Income, Net

Interest income, net consists of interest earned primarily on our cash, cash equivalents and marketable securities as well as accretion of discounts/amortization of premiums on purchases of marketable securities.

Other Income, Net

Other income, net consists of income related to an employee retention tax credit under the Coronavirus Aid, Relief, and Economic Security Act, foreign currency transaction gains and losses as well as an immaterial effect from early extinguishment of debt in connection with us paying the remaining amounts due under the SVB Loan Agreement.

Interest Expense

In August 2020, we entered into the SVB Loan Agreement under pursuant to which we borrowed $14.0 million under the SVB Term Loan. In connection with the SVB Term Loan, we recognize recognized interest expense which includes included amortization of deferred financing charges, accretion of loan discount-financing costs, accrual of the final payment fee, amortization of the term loan discount-interest and the stated interest on the SVB Term Loan. Prior to the Third Amendment to the SVB Loan Agreement that we entered into with SVB in April 2022, or the Third Amendment, the

SVB Term Loan bore interest at a floating rate per annum equal to the greater of (A) the prime rate plus 1.00% and (B) 4.25%. If SVB received evidence satisfactory to it that we had (i) received positive data for the Phase 2b/3 PRISM trial sufficient to advance Haduvio into a second Phase 3 clinical trial for prurigo nodularis and (ii) raised sufficient financing to fund such Phase 3 clinical trial and our operations, which we refer to together as the Phase 3 Event, the interest rate under the SVB Term Loan would be have been adjusted to a floating rate equal to the greater of (A) the prime rate plus 3.00% and (B) 6.25%.

On April 6, 2022, we entered into the Third Amendment to the SVB Loan Agreement, or the Third Amendment. Under the Third Amendment, SVB agreed that amounts outstanding under the SVB Loan Agreement would accrue interest at a floating per annum rate equal to (i) the greater of (A) the prime rate plus 1.00% and (B) 4.25%, prior to raising $45.0 million in net proceeds from the sale of equity securities, which we refer to as the 2022 Equity Event, and (ii) upon and after the occurrence of the 2022 Equity Event, the greater of (A) the prime rate plus 3.00% and (B) 6.25%. The closing of the April 2022 Private Placement constituted the 2022 Equity Event.

The SVB Term Loan required interest-only payments until March 2022. Commencing on March 1, 2022, we were required to repay the SVB Term Loan in 24 consecutive installments of principal plus monthly payments of accrued interest. All outstanding principal and accrued and unpaid interest under the SVB Term Loan and all other outstanding

---

obligations with respect to the SVB Term Loan are were due and payable in full on February 1, 2024. On May 9, 2023, we paid the remaining amount due under the SVB Loan Agreement, resulting in the full extinguishment of the SVB Term Loan. The total payoff amount was $6.5 million, consisting of the remaining principal amount due of $5.2 million, the final payment fee of $1.2 million, and $0.1 million of accrued interest and prepayment premium.

Change in Fair Value of Term Loan Derivative Liability

Before it was amended by the Third Amendment, the SVB Loan Agreement provided that upon the occurrence of the Phase 3 Event, as described below, the interest rate on the SVB Term Loan would increase by 2.00%. This contingent interest rate increase represented a free-standing financial instrument. Accordingly, we accounted for the contingent interest rate increase as a derivative under Accounting Standards Codification, or ASC, 815, *Derivatives and Hedging* and therefore, we recorded a term loan derivative liability for the contingent interest rate increase at its fair value. We adjusted this liability to fair value at each reporting date it remained outstanding. We recognized changes in the fair value of this term loan derivative in our statements of comprehensive loss as a component of other income (expense), net.

Results of Operations

Comparison of the Years Ended December 31, 2022 December 31, 2023 and 2021 2022

The following table summarizes our results of operations for the periods indicated (in thousands):

	Year Ended December 31,		
	2022	2021	Change
Operating expenses:			
Research and development	$ 19,834	$ 22,984	$ (3,150)
General and administrative	10,073	9,492	581
Total operating expenses	29,907	32,476	(2,569)
Loss from operations	(29,907)	(32,476)	2,569
Other income (expense):			
Change in fair value of term loan derivative liability	(147)	82	(229)
Other income (expense), net	289	(375)	664
Interest income, net	1,740	10	1,730
Interest expense	(1,163)	(1,202)	39
Total other income (expense), net	719	(1,485)	2,204
Loss before income taxes	(29,188)	(33,961)	4,773
Income tax benefit	36	21	15
Net loss	$ (29,152)	$ (33,940)	$ 4,788

	Year Ended December 31,		
	2023	2022	Change
Operating expenses:			
Research and development	$ 23,683	$ 19,834	$ 3,849
General and administrative	10,240	10,073	167
Total operating expenses	33,923	29,907	4,016
Loss from operations	(33,923)	(29,907)	(4,016)
Other income (expense):			
Interest income, net	4,748	1,740	3,008
Other income, net	469	289	180
Interest expense	(391)	(1,163)	772
Change in fair value of term loan derivative liability	—	(147)	147
Total other income, net	4,826	719	4,107
Loss before income taxes	(29,097)	(29,188)	91

Income tax benefit	32	36	(4)
Net loss	$ (29,065)	$ (29,152)	$ 87

Operating Expenses

Research and Development Expenses

The following table summarizes our research and development expenses for the periods indicated (in thousands):

	Year Ended December 31,			Year Ended December 31,		
	2022	2021	Change	2023	2022	Change
Clinical development expenses	$ 11,796	$ 15,764	$ (3,968)	$ 13,733	$ 11,796	$ 1,937
Personnel and related expenses	4,180	4,439	(259)	4,762	4,180	582
Consulting expenses and professional fees	2,595	1,761	834			
Consultant services in support of clinical development				3,829	2,595	1,234
Stock-based compensation expenses	815	743	72	871	815	56
Other research and development expenses	448	277	171	488	448	40
Total research and development expenses	$ 19,834	$ 22,984	$ (3,150)	$ 23,683	$ 19,834	$ 3,849

Research and development expenses for the year ended December 31, 2022 decreased $3.2 million December 31, 2023 increased $3.8 million, or 13.7% 19.4%, to $19.8 million $23.7 million from $23.0 million $19.8 million for the year ended December 31, 2021 December 31, 2022, primarily due to increased clinical trial costs in our Phase 2b CORAL trial and our Phase 2a RIVER trial, both of which started in 2023. Consultant services and personnel-related expenses in support of these studies also increased. These increases were partially offset by decreased clinical trial costs in our completed Phase 2b/3 PRISM trial and Phase 2 CANAL trial due to the completion of the blinded portion of the trials in 2022 and decreased personnel-related expenses primarily due to severance in the prior year period that did not recur. These decreases were partially offset by an increase in startup activities for our planned trials including purchases of clinical trial supplies as well as increased consulting expenses and professional fees that included recruiting fees related to hires in the current year, regulatory medical writing and trial design consulting fees. decreased purchases of active drug substance. For the years ended December 31, 2022 December 31, 2023 and 2021, 2022, all of our research and development expenses related to our development activity for Haduvio.

General and Administrative Expenses

General and administrative expenses for the year ended December 31, 2022 December 31, 2023 increased $0.6 million $0.1 million, or 6.1% 1.7%, to $10.1 million $10.2 million from $9.5 million $10.1 million for the year ended December 31, 2021 December 31, 2022. The increase was primarily due to higher market research costs, an increase in personnel-related expenses and higher legal, accounting and tax professional fees, which were partially offset by lower stock-based compensation expense as a result of the vesting of higher valued awards in the prior year as compared to lower valued awards granted in the current year.

Other Income, (Expense), Net

Other income, net for the year ended December 31, 2022 was December 31, 2023 increased by $4.1 million, or 571.2% to $4.8 million from $0.7 million compared to other expense, net of $1.5 million for the year ended December 31, 2021 December 31, 2022. The change increase was primarily due to an increase in interest income of $1.7 million $3.0 million due to higher cash equivalent and marketable securities balances and higher interest rate yields. In addition, during the year ended December 31, 2022, we recorded $0.3 million in other income, net related to a tax credit against employment taxes for certain previous periods provided under the CARES Act. No income was recorded related to tax credits under the CARES Act in 2021. In addition, during the year ended December 31, 2021, we recorded a $0.4 million expense related Contributing to the value increase was a reduction in interest expense of $0.8 million due to the early payoff of the shares of our common stock that we issued to Lincoln Park as consideration for Lincoln Park's commitment to purchase shares of our common stock under the LPC Purchase Agreement. This expense did not recur during the year ended December 31, 2022. These changes were partially offset by an increase SVB Term Loan in expense of $0.2 million attributable to expense being recognized during the year ended December 31, 2022 for the change in fair value and settlement of the term loan derivative liability. May 2023.

Liquidity and Capital Resources

Since our inception, we have not generated any revenue and have incurred significant operating losses and negative cash flows from our operations. Prior to the completion of our IPO, and concurrent private placement in May 2019, we financed our operations primarily through private placements of our preferred stock and convertible notes as well as borrowings under our prior term loan. From inception to our IPO, we raised an aggregate of $102.2 million in gross proceeds from sales of our preferred stock and convertible notes and borrowed $15.0 million under our a prior term loan.

In May 2019, we issued and sold 5,500,000 shares of common stock in our IPO and 1,500,000 shares of common stock in a concurrent private placement, in each case at an offering price of $10.00 per share, for combined net proceeds of

$62.1 million after deducting aggregate underwriting discounts and commissions and private placement agent fees of $4.9 million and other offering expenses of $3.0 million.

In June 2020, we entered into the ATM Sales Agreement, under which we may were able to issue and sell shares of common stock, from time to time, having an aggregate offering price of up to $12.0 million. In May 2022, we and SVB Securities amended the ATM Sales Agreement with SVB Securities to increase the maximum aggregate offering price of common stock that we may were able to issue and sell from time to time under the ATM Sales Agreement by $50.0 million, from $12.0 million to up to $62.0 million. Sales of common stock under the ATM Sales Agreement may were able to be made by any method that was deemed an "at-the-market" offering as defined in Rule 415(a)(4) under the Securities Act of 1933, as amended. We were not obligated to make any sales of our common stock under the ATM Sales Agreement. We began making sales pursuant to the ATM Sales Agreement in July 2020 and through August 15, 2023, the date of termination of the ATM Sales Agreement, we had issued and sold an aggregate of 4,333,394 shares of common stock for gross proceeds of $12.7 million, before deducting estimated commissions and allocated fees of $1.0 million.

In June 2023, we filed with the SEC the Shelf Registration Statement, which allows us to offer and sell up to $200.0 million of common stock, preferred stock, debt securities, units and/or warrants from time to time pursuant to one or more offerings at prices and terms to be determined at the time of sale. The Shelf Registration Statement was filed to replace our prior universal shelf registration statement on Form S-3 and was declared effective on August 15, 2023. Further, in June 2023, we entered into the 2023 ATM Sales Agreement with Leerink Partners, under which we may issue and sell shares of common stock, from time to time by any method that is deemed an

"at-the-market" "at-the-market" offering as defined in Rule 415(a)(4) under the Securities Act of 1933, as amended. We are not obligated to make any sales of our common stock under the 2023 ATM Sales Agreement. We began making filed a prospectus under the Shelf Registration Statement for the offer and sale of shares of our common stock having an aggregate offering price of up to $75.0 million pursuant to the 2023 ATM Sales Agreement. In accordance with the terms of the 2023 ATM Sales Agreement, the ATM Sales Agreement terminated upon effectiveness of the Shelf Registration Statement, at which point we were no longer able to issue and sell shares of our common stock under the ATM Sales Agreement. As of December 31, 2023, we had not made any sales pursuant to the 2023 ATM Sales Agreement in July 2020 and as of December 31, 2022, we had issued and sold an aggregate of 3,583,394 shares of common stock for gross proceeds of $11.0 million, before deducting estimated commissions and allocated fees of $0.8 million.Agreement.

On June 18, 2021, we entered into the LPC Purchase Agreement with Lincoln Park for an equity line financing. The LPC Purchase Agreement provides provided that, subject to the terms and conditions set forth therein, we have had the right, but not the obligation, to sell to Lincoln Park and Lincoln Park is was obligated to purchase up to $15.0 million of shares of common stock, at our sole discretion, over a 24-month period commencing on July 23, 2021. We filed a registration statement on Form S-1 covering the resale of shares of common stock that are issued to Lincoln Park under the LPC Purchase Agreement, which was declared effective on July 14, 2021. As part of the LPC Purchase Agreement, we We issued 170,088 shares of our common stock to Lincoln Park as consideration for its commitment to purchase shares of our common stock under the LPC Purchase Agreement. Under the terms As of the October 2021 Private Placements, we

agreed July 23, 2023, no shares had been sold to not issue or sell additional shares under Lincoln Park and the LPC Purchase Agreement on or prior to April 6, 2023. terminated by its terms.

SVB Loan Agreement

In August 2020, we entered into the SVB Loan Agreement with SVB, pursuant to which SVB provided the SVB Term Loan in the original principal amount of $14.0 million. Prior to the Third Amendment, the SVB Term Loan bore interest at a floating rate per annum equal to the greater of (A) the prime rate plus 1.00% and (B) 4.25%. If SVB received evidence satisfactory to it that we had (i) received positive data for the Phase 2b/3 PRISM trial, sufficient to advance Haduvio into a second Phase 3 clinical trial for prurigo nodularis and (ii) raised sufficient financing to fund such Phase 3 clinical trial and our operations, the interest rate under the SVB Term Loan would have been adjusted to a floating rate equal to the greater of (A) the prime rate plus 3.00% and (B) 6.25%. Commencing on March 1, 2022 and on the first business day of each month thereafter, we were required to repay the SVB Term Loan in 24 consecutive installments of principal plus monthly payments of accrued interest. All outstanding principal and accrued and unpaid interest under the SVB Term Loan and all other outstanding obligations with respect to the SVB Term Loan are due and payable in full on February 1, 2024. The SVB Loan Agreement permits voluntary prepayment of all, but not less than all, of the SVB Term Loan, subject to a prepayment premium. Such prepayment premium would be 3.00% of the principal amount of the SVB Term Loan if prepaid prior to the first anniversary of the date on which we entered into the SVB Term Loan or the Effective Date, 2.00% of the principal amount of the SVB Term Loan if prepaid on or after the first anniversary of the Effective Date, but prior to the second anniversary of the Effective Date and 1.00% of the principal amount of the SVB Term Loan if prepaid on or after the second anniversary of the Effective Date but prior to February 1, 2024. Upon repayment in full of the SVB Term Loan, we will be required to pay a final payment fee equal to $1.2 million. The SVB Term Loan and related obligations under the SVB Loan Agreement are secured by substantially all of our properties, rights and assets, except for our intellectual property (which is subject to a negative pledge under the SVB Loan Agreement). The SVB Loan Agreement contains customary representations, warranties, events of default and covenants. The occurrence and continuation of an event of default could cause interest to be charged at the rate that is otherwise applicable plus 5.00% (unless SVB elects to impose a smaller increase) and would provide SVB with the right to accelerate all obligations under the SVB Loan Agreement and exercise remedies against us and the collateral securing the SVB Term Loan and other obligations under the SVB Loan Agreement, including foreclosure against assets securing the SVB Term Loan and other obligations under the SVB Loan Agreement, including our cash. 89

On July 6, 2021, we and SVB entered into the First Amendment to the SVB Loan Agreement, or the First Amendment. The First Amendment modified the conditions under which we were required to cash collateralize outstanding amounts owed to SVB under the SVB Loan Agreement. Under the First Amendment, if we failed to receive positive data in our Phase 2b/3 PRISM trial or, prior to June 30, 2022, failed to raise sufficient net proceeds from the sale of equity securities to finance our

planned second Phase 3 clinical trial of Haduvio for prurigo nodularis and our ongoing operations, each of which we refer to as a Milestone Condition, we would have been required to deposit unrestricted and unencumbered cash equal to 100% of all outstanding amounts owed to SVB in a cash collateral account with SVB, which could have been used by SVB to prepay the SVB Term Loan at any time. In addition, the First Amendment provided that if we failed to maintain at least $20.0 million in unrestricted and unencumbered cash in our accounts with SVB, or the Minimum Required Cash, at any time prior to the satisfaction of all the Milestone Conditions, we would have been required to cash collateralize all outstanding amounts owed to SVB under the SVB Loan Agreement. We would also have been required to cash collateralize all outstanding amounts owed to SVB under the SVB Loan Agreement if we did not raise at least $15.0 million in net proceeds from the sale of equity securities during the period from June 1, 2021 through October 31, 2021. We satisfied this equity funding condition through a combination of equity issuances under our ATM Sales Agreement and the proceeds from the October 2021 Private Placements.

On April 6, 2022, we entered into the Third Amendment to the SVB Loan Agreement. The Third Amendment principally modified the conditions under which we are required to cash collateralize all outstanding amounts owed to SVB

under the SVB Loan Agreement. Under the terms of the Third Amendment, upon the closing of the April 2022 Private Placement, our obligations to achieve the Milestone Conditions and maintain the Minimum Required Cash terminated and the sole remaining cash collateralization requirement under the SVB Loan Agreement was the requirement that we receive positive final data by December 31, 2022 from either our Phase 2b/3 PRISM trial of Haduvio for prurigo nodularis or our Phase 2 CANAL trial of Haduvio for the treatment of chronic cough in adults with IPF. On August 3, 2022, SVB confirmed that the reported data from the Phase 2b/3 PRISM trial satisfied the requirement for positive data and that the cash collateralization requirements of the SVB Loan Agreement were no longer in effect.

In addition, the Third Amendment modified the interest rate on the principal amount outstanding under the SVB Loan Agreement, as discussed above under “—Components of Operating Results—Operating Expenses—Interest Expense.”

Cash Flows

The following table summarizes our cash flows for each of the periods presented below (in thousands):

	Year Ended December 31,		
	2022	2021	Change
Net cash used in operating activities	$ (28,175)	$ (28,946)	$ 771
Net cash used in investing activities	(107,373)	—	(107,373)
Net cash provided by financing activities	111,307	20,775	90,532
Net decrease in cash and cash equivalents	$ (24,241)	$ (8,171)	$ (16,070)

	Twelve Months Ended December 31,

	2023	2022	Change
Net cash used in operating activities	$ (31,710)	$ (28,175)	$ (3,535)
Net cash provided by (used in) investing activities	59,428	(107,373)	166,801
Net cash (used in) provided by financing activities	(7,910)	111,307	(119,217)
Net increase (decrease) in cash and cash equivalents	$ 19,808	$ (24,241)	$ 44,049

Operating Activities

During the year ended December 31, 2023, operating activities used $31.7 million of net cash, resulting from our net loss of $29.1 million and changes in our operating assets and liabilities of $3.8 million, partially offset by net non-cash charges of $1.2 million. Changes in our operating assets and liabilities for the year ended December 31, 2023 consisted primarily of a $2.9 million increase in prepaid expenses and other current assets and a $1.0 million decrease in accounts payable. The increase in prepaid expenses and other current assets was primarily due to an increase in prepayments related to our clinical trial work performed by our CROs. The decrease in accounts payable was primarily due to the timing of vendor invoices. The non-cash charges consisted primarily of stock-based compensation expense of $2.2 million, $0.4 million for the write off of deferred offering costs, $0.4 million change in value of our operating lease right-of-use assets and liabilities and $0.2 million of accretion/accrual of term loan discounts and debt issuance costs, which were partially offset by $2.1 million of accretion of our available-for-sale marketable securities.

During the year ended December 31, 2022, operating activities used $28.2 million of net cash, resulting from our net loss of $29.2 million, changes in our operating assets and liabilities of $1.2 million partially offset by non-cash charges of $2.2 million. Changes in our operating assets and liabilities for the year ended December 31, 2022 consisted of a $0.6 million increase in prepaid expenses and other current assets and a $0.6 million decrease in accrued expenses and other liabilities. The increase in prepaid expenses and other current assets was primarily due to an increase in interest income receivable related to our marketable securities. The decrease in accrued expenses and other liabilities was primarily due to decreased accruals for research, development and clinical trial work performed by our CROs. The non-cash charges for the year ended December 31, 2022 consisted primarily of stock-based compensation expense of $2.3 million and $0.5 million of accretion/accrual of term loan discounts and debt issuance costs offset by $0.8 million of accretion of our available-for-sale marketable securities.

Investing Activities

During the year ended December 31, 2021 December 31, 2023, operating activities used $28.9 million of net cash resulting provided by investing activities was $59.4 million, consisting of $69.5 million of proceeds from our net loss maturities of $33.9 million, available-for-sale marketable securities partially offset by changes in our operating assets $9.9 million of purchases of available-for-sale marketable securities and liabilities $0.1 million of $1.5 million purchases of property, equipment and non-cash charges of $3.5 million. Changes in our operating assets and liabilities for the year ended December 31, 2021 consisted of a $0.3 million decrease in prepaid expenses and other current assets, a $0.8 million increase in accounts payable and a $0.3 million decrease in accrued expenses. The decrease in prepaid expenses and other current assets was primarily due to the return of a

deposit associated with the completion of one of our clinical trials. The increase in accounts payable was primarily due to timing of vendor invoices. The decrease in accrued expenses and other liabilities was primarily due to decreased accruals related to non-income based taxes and accrued consulting and professional fees partially offset by increased accruals for research, development and clinical trial work performed by our CROs. The non-cash charges for the year ended December 31, 2021 consisted primarily of stock-based compensation expense of $2.5 million, $0.6 million of accretion/accrual of term loan discounts and debt issuance costs and $0.4 million of other expense associated with the value of the shares of our common stock that we issued to Lincoln Park as consideration for Lincoln Park's commitment to purchase shares of our common stock under the LPC Purchase Agreement.

Investing Activitiesleasehold improvements.

During the year ended December 31, 2022, net cash used in investing activities was $107.4 million, primarily related to purchases of and proceeds from maturities of available-for-sale marketable securities.

Financing Activities

During the year ended December 31, 2021 December 31, 2023, no net cash was used in or provided financing activities was $7.9 million, consisting of repayments of $9.4 million on the SVB Term Loan including payment of the final payment fee and prepayment premium, both associated with the payoff of the SVB Term Loan, payments of offering costs of $0.3 million and payments of $0.1 million on our finance lease. These cash outflows were partially offset by investing activities.

Financing Activitiesgross cash proceeds of $1.7 million, net of commissions from sales of our common stock under the ATM Sales Agreement, $0.1 million of cash proceeds from the exercise of stock options and $0.1 million of cash proceeds from sales under our 2019 Employee Stock Purchase Plan.

During the year ended December 31, 2022, net cash provided by financing activities was $111.3 million, primarily consisting of net cash proceeds from our April 2022 Private Placement and our September 2022 Offering of $105.4 million, cash proceeds of $11.8 million from the exercise of warrants and cash proceeds from the exercise of stock options of $0.1 million, partially offset by repayments of $5.8 million on the SVB Term Loan and payments of offering costs of $0.2 million. 87

During the year ended December 31, 2021, net cash provided by financing activities was $20.8 million, primarily consisting of net cash proceeds from our October 2021 Private Placements of $13.7 million and cash proceeds of $7.5 million, net of commissions, from sales of our common stock under the ATM Sales Agreement, partially offset by payments of offering costs of $0.4 million and payments of financing costs of $0.1 million associated with the First Amendment to the SVB Loan Agreement. 90

Funding Requirements

We expect to incur substantial expenditures in the foreseeable future as we advance Haduvio through clinical development, the regulatory approval process and, if approved, commercial launch activities. Specifically, in the near term, we expect to incur substantial expenses relating to:

- the next trials we plan to conduct for our Phase 2b CORAL clinical trial of Haduvio for the treatment of chronic cough in adults with IPF;
- our planned Phase 2 1b clinical trial to evaluate the effect of Haduvio on respiratory physiology in patients with IPF of varying disease severity;
- our Phase 2a RIVER clinical trial of Haduvio for the treatment of refractory chronic cough; RCC; and
- the second part of our ongoing HAL study. HAP study to further characterize the abuse potential of oral nalbuphine.

Generally, regulatory authorities require two adequate and well-controlled studies for approval. Furthermore, we We expect to continue to incur costs associated with operating as a public company, including significant legal, accounting, investor relations and other expenses.

We will need substantial additional funding to support our continuing operations and pursue our growth strategy. operations. Until such time as we can generate significant revenue from sales of Haduvio, if ever, we expect to finance our operations through public or private equity offerings, debt financings, collaborations and licensing arrangements or other sources to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms or at all. Our future funding requirements, both short-term and long-term, will depend on many factors, including:

- the scope, progress, timing, costs and results of clinical trials of Haduvio, including the next our Phase 2b CORAL clinica trials trial of Haduvio for the treatment of chronic cough in adults with IPF, our planned Phase 2 1b trial to evaluate the ef of Haduvio on respiratory physiology in patients with IPF of varying disease severity, our Phase 2a RIVER clinical trial ir refractory chronic cough, RCC, and the second part of our ongoing HAL HAP study, as well as trials for any future produ candidates;
- the number and characteristics of indications for which we seek to develop Haduvio or any future product candidates an their respective development requirements;
- the outcome, timing and costs of clinical and nonclinical trials and of seeking regulatory approvals, including the costs o supportive clinical studies such as our ongoing HAL HAP study and a potential Thorough QT TQT study;
- the costs associated with the manufacture of necessary quantities of Haduvio or any future product candidate for clinica development in connection with regulatory submissions;
- the costs of commercialization activities for Haduvio for the treatment of chronic cough in adults with IPF or any other chronic cough indications RCC or for the treatment of prurigo nodularis or for any future product candidates that receive marketing approval, if any, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities;
- subject to receipt of marketing approvals, revenue, if any, received from commercial sales of Haduvio for the treatment c chronic cough in adults with IPF or for any other chronic cough indications RCC or for the treatment of prurigo nodularis from any future product candidates;

- our ability to identify potential collaborators for Haduvio for the treatment of prurigo nodularis or for the treatment of chro cough in adults with IPF or for any other chronic cough indications RCC or for any future product candidates and the ter and timing of any collaboration agreement that we may establish for the development and any commercialization of suc product candidates;
- the extent to which we acquire or in-license rights to other potential product candidates or technologies and the terms a timing of any such acquisition or licensing arrangements;
- our potential obligation to make milestone payments to Endo Pharmaceuticals Inc., or Endo, which would become due upon the successful completion of the first Phase 3 clinical trial of a licensed product candidate and the marketing appro of a licensed product in the United States, as well as our potential obligations to pay Endo royalties on the net sales of t product;
- our headcount growth and associated costs as we expand our research and development activities and establish a commercial infrastructure;

- the costs of preparing, filing and prosecuting patent applications, maintaining, expanding and protecting our intellectual property rights and defending against intellectual property-related claims;
- the effect of competing technologies and market developments;
- our ability to establish and maintain healthcare coverage and adequate reimbursement for our products; and

---

- the costs of operating as a public company; and
- the impact of the COVID-19 pandemic and other outbreaks of infectious disease on the scope, progress, timing, co and results of our ongoing and planned clinical trials of Haduvio. company.

We believe that our existing cash, cash equivalents and marketable securities, will enable us to fund our operating expenses and capital expenditure requirements into 2026. Our current plans do not take into account the cost of any additional clinical trials for the treatment of prurigo nodularis.

We have based our estimates as to how long we expect we will be able to fund our operations on assumptions that may prove to be wrong and we could use our available capital resources sooner than we currently expect, in which case we would be required to obtain additional financing and financing may not be available to us on acceptable terms, on a timely basis or at all. Our failure to raise capital as and when needed would have a negative impact on our financial condition and our ability to pursue our business strategy.

We do not have any committed external source of funds. Accordingly, we will be required to obtain further funding through public or private equity offerings, debt financings, collaborations, licensing arrangements or other sources to complete the clinical development and commercialization of Haduvio for the treatment of chronic cough in adults with IPF or refractory chronic cough RCC or for the treatment of prurigo nodularis or any other indication. If we raise additional funds by issuing equity securities, our stockholders may experience dilution. Any debt financing into which we enter would result in fixed payment obligations and may involve agreements that include grants of security interests on our assets and restrictive covenants that limit our ability to take specific actions, such as incurring additional debt, making capital expenditures, granting liens over our assets, redeeming stock or declaring dividends, that could adversely impact our ability to conduct our business. For example, in connection with the SVB Term Loan, we granted a security interest on all of our assets, excluding our intellectual property, agreed to a negative pledge on our intellectual property, agreed to restrictive covenants including, subject to certain exceptions, covenants that prohibit us from transferring all or any part of our business or property, changing our business, liquidating or dissolving, merging with or acquiring another entity, entering into a transaction that will result in a change in control, incurring additional indebtedness, creating any lien on our property, paying dividends or redeeming stock, making payments on subordinated debt or entering into material transactions with affiliates and agreed to cash collateralize the SVB Term Loan in certain circumstances. Future debt securities or other financing arrangements could contain similar or more restrictive negative covenants. In addition, securing financing could require a substantial amount of time and attention from our management and may divert a disproportionate amount of their attention away from day-to-day activities, which may adversely affect our management's ability to oversee the development of our product candidates. Any debt financing that we seek or additional equity that we raise may contain terms that could adversely affect our common stockholders.

If we are unable to raise sufficient capital as and when needed, we may be required to delay, reduce or abandon our product development programs or commercialization efforts. If we raise additional funds through collaborations or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to future revenue streams or product candidates or grant licenses on terms that may not be favorable to us.

Contractual Obligations and Commitments

A significant portion of our development activities are outsourced to third parties under agreements, including with CROs and contract manufacturers in connection with the production of clinical trial materials. The contracts are cancelable at any time by us, generally upon 60 days' prior written notice to the CRO, and therefore we believe that our non-cancelable obligations under these agreements are not material.

For information related to our future commitments relating to our lease and licensing agreements, see Note 5, "Leases" and Note 12, "Collaborative and Licensing Agreements" of our Consolidated Financial Statements.

Critical Accounting Policies and Use of Estimates

Our financial statements Consolidated Financial Statements have been prepared in accordance with U.S. generally accepted accounting principles. The preparation of these financial statements Consolidated Financial Statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, Consolidated Financial Statements, as well as the

reported expenses incurred during the reporting periods. Our estimates are based on our historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in the Notes to our financial statements, we We believe that the following estimates and assumptions involved in the accounting policy described below may have the greatest potential impact on our Consolidated Financial Statements and, therefore, consider this to be our critical accounting policies are most important to understanding and evaluating our reported financial results. policy.

Research and Development Expenses

Research and development costs are expensed as incurred. Nonrefundable advance payments for goods or services that will be used or rendered for future research and development activities are deferred and capitalized and recognized as an expense as the goods are delivered or the related services are performed.

We have entered into agreements with CROs, contract manufacturing organizations and other companies that provide services in connection with our research and development activities. Our research and development accruals are estimated based on the level of services performed, progress of the studies, including the phase or completion of events, and

contracted costs. The estimated costs of research and development provided, but not yet invoiced, are included in accrued expenses on our consolidated balance sheet. If the actual timing of the performance of services or the level of effort varies from the original estimates, we will adjust the accrual accordingly. Payments made to CROs, contract manufacturing organizations and other companies under these arrangements in advance of the performance of the related services are recorded as prepaid expenses.

Stock-Based Compensation Expense

We account for stock-based compensation arrangements with employees and non-employees for consultancy services in accordance with ASC 718, *Stock Compensation*, or ASC 718. ASC 718 requires the recognition of compensation expense, using a fair value-based method, for costs related to all stock-based payments, including stock options. Our determination of the fair value of stock options on the date of grant utilizes the Black-Scholes option pricing

model for stock options with time-based vesting and is impacted by our common stock price as well as changes in assumptions regarding a number of complex and subjective variables. These variables include the expected term that options will remain outstanding, expected common stock price volatility over the term of the option awards, risk-free interest rates and expected dividends.

The fair value of an option award is recognized over the period during which the optionee is required to provide services in exchange for the option award, known as the requisite service period (usually the vesting period) on a straight-line basis. Forfeitures are accounted for as they occur.

Estimating the fair value of equity-settled awards as of the grant date using valuation models, such as the Black-Scholes option pricing model, is affected by assumptions regarding a number of complex variables. Changes in the assumptions can materially affect the fair value and ultimately how much stock-based compensation expense is recognized. These inputs are subjective and generally require analysis and judgment to develop.

Expected Term—The expected term assumption represents the weighted average period that the stock-based awards are expected to be outstanding. We have elected to use the “simplified method” for estimating the expected term of the options, whereby the expected term equals the arithmetic average of the vesting term and the original contractual term of the option.

Expected Volatility—For all stock options granted to date, the volatility data was estimated based on a study of publicly traded industry peer companies. For purposes of identifying these peer companies, we considered the industry, stage of development, size and financial leverage of potential comparable companies.

Expected Dividend—The Black-Scholes valuation model calls for a single expected dividend yield as an input. We currently have no history or expectation of paying cash dividends on our common stock.

Risk-Free Interest Rate—The risk-free interest rate is based on the yield available on U.S. Treasury zero-coupon issues similar in duration to the expected term of the equity-settled award.

We will continue to use judgment in evaluating the expected volatility, expected terms and interest rates utilized for our stock-based compensation expense calculations on a prospective basis.

Income Taxes

We provide for income taxes under the asset and liability method. Current income tax expense or benefit represents the amount of income taxes expected to be payable or refundable for the current year. Deferred income tax assets and liabilities are determined based on differences between the financial statement reporting and tax bases of assets and liabilities and net operating loss and credit carryforwards and are measured using the enacted tax rates and laws that will be in effect when such items are expected to reverse. Deferred income tax assets are reduced, as necessary, by a valuation allowance when management determines it is more likely than not that some or all of the tax benefits will not be realized.

We account for uncertain tax positions in accordance with ASC 740, *Accounting for Uncertainty in Income Taxes*, or ASC 740. We assess all material positions taken in any income tax return, including all significant uncertain positions, in all tax years that are still subject to assessment or challenge by relevant taxing authorities. Assessing an uncertain tax

position begins with the initial determination of the position's sustainability and is measured at the largest amount of benefit that is greater than fifty percent likely of being realized upon ultimate settlement. As of each balance sheet date, unresolved uncertain tax positions must be reassessed, and we will determine whether (i) the factors underlying the sustainability assertion have changed and (ii) the amount of the recognized tax benefit is still appropriate. The recognition and measurement of tax benefits requires significant judgment. Judgments concerning the recognition and measurement of a tax benefit might change as new information becomes available.

Warrants

We determine the accounting classification of warrants that are issued, as either liability or equity, by first assessing whether the warrants meet liability classification in accordance with ASC 480, *Distinguishing Liabilities from Equity*, and then in accordance with ASC 815, *Derivatives and Hedging*, depending on the specific terms of the warrant agreement. Under ASC 480, warrants are considered liability classified if the warrants are mandatorily redeemable, obligate the issuer to settle the warrants or the underlying shares by paying cash or other assets, or must or may require settlement by issuing a variable number of shares.

If warrants do not meet liability classification under ASC 480, we assess the requirements under ASC 815, which states that contracts that require or may require the issuer to settle the contract for cash are liabilities recorded at fair value, irrespective of the likelihood of the transaction occurring that triggers the net cash settlement feature. If the warrants do not require liability classification under ASC 815, in order to conclude equity classification, we assess whether the warrants are indexed to our common stock and whether the warrants are classified as equity under ASC 815 or other applicable GAAP. After all relevant assessments are made, we conclude whether the warrants are classified as liability or equity. Liability classified warrants are required to be accounted for at fair value both on the date of issuance and on subsequent accounting period ending dates, with all changes in fair value after the issuance date recorded in the statements of comprehensive loss as a gain or loss. For equity classified warrants, no changes in fair value are recognized after the issuance date.

Fair Value Measurements

Our financial instruments have consisted of cash and cash equivalents, tax credit and other receivables, accounts payable, accrued expenses, term loans, term loan derivative liability and warrants to acquire our common stock. Fair value estimates of these instruments are made at a specific point in time, based on relevant market information. The carrying amounts of cash and cash equivalents, tax credit and other receivables, accounts payable and accrued expenses are generally considered to be representative of their respective fair values because of the short-term nature of those instruments. Available-for-sale marketable securities are reported at their fair values, based upon pricing of securities with the same or similar investment characteristics as provided by third-party pricing services, as described below. The carrying amount of the term loan approximates its fair value due to its floating market-based interest rate. The carrying amount of the term loan approximates its fair value due to its floating market-based interest rate. The fair value of the term loan derivative liability is estimated utilizing a probability-weighted cash flow approach.

Current accounting guidance defines fair value, establishes a framework for measuring fair value in accordance with ASC 820, *Fair Value Measurements and Disclosures*, and requires certain disclosures about fair value measurements. The valuation techniques included in the guidance are based on observable and unobservable inputs. Observable inputs reflect readily obtainable data from independent sources, while unobservable inputs reflect market assumptions and are classified into the following fair value hierarchy:

- Level 1—Observable inputs—quoted prices in active markets for identical assets and liabilities.
- Level 2—Observable inputs other than the quoted prices in active markets for identical assets and liabilities—such a quoted prices for similar instruments, quoted prices for identical or similar instruments in inactive markets, or other inputs that are observable or can be corroborated by observable market data.
- Level 3—Unobservable inputs—includes amounts derived from valuation models where one or more significant inpu are unobservable and require the company to develop relevant assumptions.

Valuation Techniques - Level 2 Inputs

We estimate the fair values of our financial instruments categorized as level 2 in the fair value hierarchy, including U.S. Treasury securities, U.S. government agency obligations, corporate bonds, commercial paper and municipal bonds, by taking into consideration valuations obtained from third-party pricing services. The pricing services use industry standard valuation models, including both income- and market-based approaches, for which all significant inputs are observable, either directly or indirectly, to estimate fair value. These inputs include reported trades of and broker/dealer quotes on the same or similar securities, benchmark yields, issuer credit spreads, benchmark securities, and other observable inputs. We obtain a single price for each financial instrument and we do not adjust the prices obtained from the pricing service.

JOBS Act Accounting Election

The Jumpstart Our Business Startups Act of 2012, as amended, or JOBS Act, permits emerging growth companies such as us to take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

Recently Adopted Accounting Pronouncements

There have been no new pronouncements adopted during the year ended December 31, 2022, which materially impacted our Consolidated Financial Statements.

Recently Issued Accounting Pronouncements

There have been no new pronouncements issued during the year ended December 31, 2022, which could be expected to materially impact our Consolidated Financial Statements.

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

Not applicable.

Item 8. Financial Statements and Supplementary Data.

The financial statements required to be filed pursuant to this Item 8 are appended to this report. An index of those financial statements is found in Item 15 of Part IV of this Annual Report on Form 10-K.

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

None.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures.

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, evaluated the effectiveness of our disclosure controls and procedures as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, as of December 31, 2022 December 31, 2023. Our disclosure controls and procedures are designed to ensure that information we are required to disclose in the reports we file or submit under the Exchange Act is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate to allow timely decisions regarding required disclosures, and is recorded, processed, summarized, and reported within the time periods specified in the SEC's rules and forms. Our management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and our management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Because of the inherent limitations in all control systems, no evaluation of controls and procedures can provide absolute assurance that all control issues and instances of fraud, if any, within the Company have been detected. Based on the evaluation of our disclosure controls and procedures as of December 31, 2022 December 31, 2023, our Chief Executive Officer and Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act. Our internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with general generally accepted accounting principles. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, we conducted an evaluation of the effectiveness of our internal control over financial reporting based on the 2013 framework in Internal Control–Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on our evaluation under that framework, our management concluded that our internal control over financial reporting was effective as of December 31, 2022 December 31, 2023.

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 due to an exemption established by the Jumpstart Our Business Startups Act of 2012 for emerging growth companies.

Changes in Internal Control over Financial Reporting

No change in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) occurred during the three months ended December 31, 2022 December 31, 2023 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

None.

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

Not Applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

The information required by this Item 10 will be included in our Definitive Proxy Statement to be filed with the SEC with respect to our 2023 2024 Annual Meeting of Stockholders and is incorporated herein by reference.

Item 11. Executive Compensation.

The information required by this Item 11 will be included in our Definitive Proxy Statement to be filed with the SEC with respect to our 2023 2024 Annual Meeting of Stockholders and is incorporated herein by reference.

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

The information required by this Item 12 will be included in our Definitive Proxy Statement to be filed with the SEC with respect to our 2023 2024 Annual Meeting of Stockholders and is incorporated herein by reference.

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

The information required by this Item 13 will be included in our Definitive Proxy Statement to be filed with the SEC with respect to our 2023 2024 Annual Meeting of Stockholders and is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services.

The information required by this Item 14 will be included in our Definitive Proxy Statement to be filed with the SEC with respect to our 2023 2024 Annual Meeting of Stockholders and is incorporated herein by reference.

PART IV

Item 15. Exhibits, Financial Statement Schedules.

(1) Financial Statements

The following documents are included on pages F-1 through F-21 attached hereto and Consolidated Financial Statements are filed as part of this Annual Report on Form 10-K.

(2) Financial Statement Schedules:

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

(3) Exhibits.

The following is a list of exhibits filed as part of this Annual Report on Form 10-K.

Exhibit Number	Description
3.1	Restated Certificate of Incorporation of Trevi Therapeutics, Inc., as amended (incorporated by reference to Exhibit 3.1 to the Registrant's Current Quarterly Report on Form 8-K 10-Q (File No. 001-38886) filed with the SEC on May 9, 2019 August 10, 2023)

3.2	Amended and Restated Bylaws of Trevi Therapeutics, Inc. (incorporated by reference to Exhibit 3.2 3.1 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on May 9, 2019 April 14, 2023)
4.1	Specimen Stock Certificate evidencing the shares of common stock (incorporated by reference to Exhibit 4.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)

4.2 4.2*	Description of Registrant's Securities (incorporated by referred to Exhibit 4.2 to the Registrant's Annual Report on Form 10-K (File No. 001-38886) filed with the SEC on March 16, 2020)
4.3	Form of Pre-Funded Warrant dated October 5, 2021 (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on October 1, 2021)
4.4	Form of 7-Year Common Stock Warrant dated October 5, 2021 (incorporated by reference to Exhibit 4.2 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on October 1, 2021)
4.5	Form of 3.5-Year Common Stock Warrant dated October 5, 2021 (incorporated by reference to Exhibit 4.3 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on October 1, 2021)
4.6	Form of 7-Year Common Stock Warrant dated October 18, 2021 (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on October 19, 2021)
4.7	Form of 3.5-Year Common Stock Warrant dated October 18, 2021 (incorporated by reference to Exhibit 4.2 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on October 19, 2021)
4.8	Form of Pre-Funded Warrant (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on April 7, 2022)
4.9	Form of Pre-Funded Warrant (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on September 23, 2022)
10.1	Second Amended and Restated Investors' Rights Agreement dated as of July 14, 2017 (incorporated by reference to Exhibit 10.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
10.2+	2012 Stock Incentive Plan, as amended (incorporated by reference to Exhibit 10.2 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)

10.3+	Form of Nonstatutory Stock Option Agreement under the 2012 Stock Incentive Plan (incorporated by reference to Exhibit 10.3 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
10.4+	2019 Stock Incentive Plan (incorporated by reference to Exhibit 10.4 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
10.5+	Form of Stock Option Agreement under the 2019 Stock Incentive Plan (incorporated by reference to Exhibit 10.5 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
10.6+	2019 Employee Stock Purchase Plan (incorporated by reference to Exhibit 10.6 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
10.7+	Non-Employee Director Compensation Policy (incorporated by reference to Exhibit 10.7 to the Registrant's Annual Report on Form 10-K (File No. 001-38886) filed with the SEC on March 25, 2021)
10.8+	Trevi Therapeutics, Inc. Executive Separation Benefits and Retention Plan (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on September 24, 2019)
10.9+	Employment Agreement, dated December 4, 2012, by and between the Registrant and Jennifer L. Good (incorporated by reference to Exhibit 10.8 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
10.10+	Offer Letter, dated December 4, 2012, by and between the Registrant and Thomas R. Sciascia (incorporated by referred to Exhibit 10.10 to the Registrant's Annual Report on Form 10-K (File No. 001-38886) filed with the SEC on March 16, 2020)
10.11*+ 10.11+	Offer Letter, dated November 4, 2022, by and between the Registrant and David Clark (incorporated by reference to Exhibit 10.11 to the Registrant's Annual Report on Form 10-K (File No. 001-38886) filed with the SEC on March 16, 2023)
10.12+	Offer Letter, dated June 17, 2021, by and between the Registrant and Lisa Delfini (incorporated by reference to Exhibit 10.5 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-38886) filed with the SEC on August 12, 2021)
10.13+	Form of Indemnification Agreement between the Registrant and each of its directors and executive officers (incorporated by reference to Exhibit 10.12 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)

10.14	Indenture of Lease, dated February 6, 2013, by and between First Niagara Bank, N.A. and the Registrant (incorporated by reference to Exhibit 10.13 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)

10.15	First Amendment to Lease, dated December 5, 2017, by and between the Registrant and 195 Church Street Associates, LLC (incorporated by reference to Exhibit 10.14 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
10.16* 10.16	Second Amendment to Lease, dated November 21, 2022, by and between the Registrant and 195 Church Street Associates, LLC (incorporated by reference to Exhibit 10.16 to the Registrant's Annual Report on Form 10-K (File No. 001-38886) filed with the SEC on March 16, 2023)
10.17†	Exclusive License Agreement, dated as of May 13, 2011, by and between the Registrant and Penwest Pharmaceuticals Co. (incorporated by reference to Exhibit 10.15 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)

10.18	Share Purchase Agreement, dated as of May 6, 2019, by and between the Registrant and New Enterprise Associates 16, L.P. (incorporated by reference to Exhibit 10.17 to Amendment No. 3 to Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on May 7, 2019)
10.19	Loan and Security Agreement, dated as of August 13, 2020, between Silicon Valley Bank and Trevi Therapeutics, Inc. (incorporated by referred to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-38886) filed with the SEC on November 12, 2020)
10.20	First Amendment to Loan and Security Agreement, dated July 6, 2021, by and between Silicon Valley Bank and the Registrant (incorporated by reference to Exhibit 99.1 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on July 7, 2021
10.21	Second Amendment to Loan and Security Agreement, dated August 13, 2021, by and between Silicon Valley Bank and the Registrant (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-38886) filed with the SEC on November 10, 2021
10.22	Third Amendment to Loan and Security Agreement, dated April 6, 2022, by and between Silicon Valley Bank and the Registrant (incorporated by reference to Exhibit 99.3 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on April 7, 2022)
10.23	Purchase Agreement, dated as of June 18, 2021, by and between the Registrant and Lincoln Park Capital Fund, LLC (incorporated by reference to Exhibit 99.1 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on June 21, 2021)
10.24	Registration Rights Agreement, dated as of June 18, 2021, by and between the Registrant and Lincoln Park Capital Fund, LLC (incorporated by reference to Exhibit 99.2 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on June 21, 2021)

10.25		Form of Securities Purchase Agreement dated September 30, 2021 (incorporated by reference to Exhibit 99.1 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on October 1, 2021)
10.26	10.20	Form of Registration Rights Agreement dated September 30, 2021 (incorporated by reference to Exhibit 99.2 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on October 1, 2021)
10.27	10.21	Form of Securities Purchase Agreement dated October 15, 2021 (incorporated by reference to Exhibit 99.1 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on October 19, 2021)
10.28	10.22	Form of Registration Rights Agreement dated October 15, 2021 (incorporated by reference to Exhibit 99.2 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on October 19, 2021)
10.29	10.23	Securities Purchase Agreement, dated April 6, 2022, by and among the Registrant and the Purchasers named therein (incorporated by reference to Exhibit 99.1 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on April 7, 2022)
10.30	10.24	Registration Rights Agreement, dated April 6, 2022, by and among the Registrant and the Purchasers named therein (incorporated by reference to Exhibit 99.2 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on April 7, 2022)
10.31		Consulting Services Agreement, dated August 31, 2022, by and between the Registrant and William P. Forbes (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-38886) filed with the SEC on November 10, 2022)
10.32		Sales Agreement, dated June 26, 2020, by and between the Registrant and SVB Securities LLC (formerly SVB Leerink LLC) (incorporated by reference to Exhibit 1.1 to the Registrant's Registration Statement on Form S-3 (File No. 333-239499) filed with the SEC on June 26, 2020)
10.33		Amendment No. 1 to the Sales Agreement, dated May 13, 2022, by and between the Registrant and SVB Securities LLC (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-38886) filed with the SEC on May 13, 2022)
21.1		List of Subsidiaries (incorporated by reference to Exhibit 21.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230745) filed with the SEC on April 5, 2019)
23.1*		Consent of Ernst & Young LLP, independent registered public accounting firm
31.1*		Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002. 2002
31.2*		Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002. 2002
32.1*		Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002. 2002

32.2*		Certification of Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to

	Section 906 of the Sarbanes-Oxley Act of 2002. 2002
97*	Dodd-Frank Compensation Recovery Policy
101.INS*	XBRL Instance Document
101.SCH*	XBRL Taxonomy Extension Schema Document
101.CAL*	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF*	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB*	XBRL Taxonomy Extension Label Linkbase Document
101.PRE*	XBRL Taxonomy Extension Presentation Linkbase Document
104	104 Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101)

* Filed herewith.

+ Management contract or compensatory plan or arrangement.

† Confidential treatment has been granted as to certain portions, which portions have been omitted and filed separately with the Securities and Exchange Commission.

Item 16. Form 10-K Summary

None.

SIGNATURES

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

TREVI THERAPEUTICS, INC.

Date: March 16, 2023 March 20, 2024

By: /s/ Jennifer Good

Jennifer Good

President and Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this Report has been signed below by the following persons on behalf of the Registrant in the capacities and on the dates indicated.

Name	Title	Date
/s/ Jennifer Good **Jennifer Good**	President and Chief Executive Officer, Director (Principal Executive Officer)	March 16, 2023 20, 2024
/s/ Lisa Delfini **Lisa Delfini**	Chief Financial Officer (Principal Financial Officer)	March 16, 2023 20, 2024
/s/ Christopher Galletta **Christopher Galletta**	Controller (Principal Accounting Officer)	March 16, 2023 20, 2024
/s/ David Meeker, M.D. **David Meeker, M.D.**	Chairman of the Board	March 16, 2023 20, 2024
/s/ James V. Cassella, Ph.D. **James V. Cassella, Ph.D.**	Director	March 16, 2023 20, 2024
/s/ Dominick Colangelo **Dominick Colangelo**	Director	March 16, 2023 20, 2024
/s/ Michael Heffernan **Michael Heffernan**	Director	March 16, 2023 20, 2024
/s/ Edward Mathers **Edward Mathers**	Director	March 16, 2023 20, 2024
/s/ Anne VanLent **Anne VanLent**	Director	March 16, 2023 20, 2024

Trevi Therapeutics, Inc.

Index to Consolidated Financial Statements

Years Ended December 31, 2022 December 31, 2023 and 20212022

Contents

Report of Independent Registered Public Accounting Firm

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

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Trevi Therapeutics, Inc. (the Company) as of December 31, 2022 December 31, 2023 and 2021, 2022, the related consolidated statements of comprehensive loss, stockholders' equity and cash flows for the years then ended, and the related notes (collectively referred to as the "consolidated financial statements" "Consolidated Financial Statements"). In our opinion, the consolidated financial statements Consolidated Financial Statements present fairly, in all material respects, the financial position of the Company at December 31, 2022 December 31, 2023 and 2021, 2022, and the results of its operations and its cash flows for the years then ended, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits, we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2013.

Hartford, Connecticut

March 16, 2023 20, 2024

Trevi Therapeutics, Inc.

Consolidated Balance Sheets

(Amounts in thousands, except share and per share amounts)

	December 31, 2022	December 31, 2021	December 31, 2023	December 31, 2022
Assets				
Current assets:				
Cash and cash equivalents	$ 89,5	$ 30,8	$ 32,397	$ 12,589
Marketable securities	107,921	—	50,574	107,921
Prepaid expenses	795	886	3,621	795
Other current assets	1,311	241	955	1,311
Total current assets	122,616	37,957	87,547	122,616
Operating lease right-of-use assets			1,137	24
Other non-current assets	205	334	297	205

Operating lease right-of-use asset		13		
	24	1		
Property, equipment and leasehold improvements, net	17			
	0	53	216	170
Finance lease right-of-use assets			206	—
Total assets	12			
	3,	38		
	01	,4		
	$ 5	$ 75	$ 89,403	$ 123,015
Liabilities and stockholders' equity				
Current liabilities:				
Accounts payable	2,	2,		
	85	84		
	$ 7	$ 9	$ 1,809	$ 2,857
Accrued expenses	3,	3,		
	51	80		
	8	8	3,709	3,518
Operating lease liabilities			184	25
Finance lease liabilities			122	—
Term loan	7,	5,		
	00	83		
	0	3	—	7,000
Term loan derivative liability		11		
	—	4		
Operating lease liability		12		
	25	0		
Total current liabilities	13	12		
	,4	,7		
	00	24	5,824	13,400
Operating lease liabilities			1,001	2
Finance lease liabilities			31	—
Term loan	2,	8,		
	15	65		
	1	2	—	2,151
Operating lease liability	2	24		

Other non-current liabilities	3	—	—	3
Total liabilities	15,556	21,400	6,856	15,556
Commitments and contingencies (Note 13)				
Stockholders' equity:				
Preferred stock: $0.001 par value; 5,000,000 shares authorized at December 31, 2022 and December 31, 2021; no shares issued or outstanding at December 31, 2022 and December 31, 2021.	—	—		
Common stock: $0.001 par value; 200,000,000 shares authorized at December 31, 2022 and December 31, 2021; and 59,943,430 and 28,505,804 shares issued and outstanding at December 31, 2022 and December 31, 2021, respectively.	60	29		
Preferred stock: $0.001 par value; 5,000,000 shares authorized at December 31, 2023 and December 31, 2022; no shares issued or outstanding at December 31, 2023 and December 31, 2022.			—	—
Common stock: $0.001 par value; 200,000,000 shares authorized at December 31, 2023 and December 31, 2022; and 68,283,699 and 59,943,430 shares issued and outstanding at December 31, 2023 and December 31, 2022, respectively.			68	60
Additional paid-in capital	317,590	319,796	321,642	317,590
Accumulated other comprehensive loss	(122)	—	(29)	(122)
Accumulated deficit	(210,069)	(180,969)	(239,134)	(210,069)
Total stockholders' equity	107,459	317,075	82,547	107,459

Total liabilities and stockholders' equity	12 3, 01 $ 5	38 ,4 $ 75	$ 89,403	$ 123,015

See accompanying notes.

Trevi Therapeutics, Inc.

Consolidated Statements of Comprehensive Loss

(Amounts in thousands, except share and per share amounts)

	Year Ended December 31,		Year Ended December 31,	
	2022	2021	2023	2022
Operating expenses:				
Research and development	$ 19,834	$ 22,984	$ 23,683	$ 19,834
General and administrative	10,073	9,492	10,240	10,073
Total operating expenses	29,907	32,476	33,923	29,907
Loss from operations	(29,907)	(32,476)	(33,923)	(29,907)
Other income (expense):				
Interest income, net			4,748	1,740
Other income, net			469	289
Interest expense			(391)	(1,163)
Change in fair value of term loan derivative liability	(147)	82	—	(147)
Other income (expense), net	289	(375)		
Interest income, net	1,740	10		
Interest expense	(1,163)	(1,202)		
Total other income (expense), net	719	(1,485)		
Total other income, net			4,826	719
Loss before income taxes	(29,188)	(33,961)	(29,097)	(29,188)

Income tax benefit	36	21	32	36
Net loss	$ (29,152)	$ (33,940)	$ (29,065)	$ (29,152)
Basic and diluted net loss per common share outstanding	$ (0.45)	$ (1.49)	$ (0.29)	$ (0.45)
Weighted average common shares used in net loss per share attributable to common stockholders, basic and diluted	64,541,911	22,841,481	99,033,373	64,541,911
Net loss	$ (29,152)	$ (33,940)	$ (29,065)	$ (29,152)
Other comprehensive loss:				
Net unrealized losses on available-for-sale marketable securities	(122)	—		
Net unrealized gains (losses) on available-for-sale marketable securities			93	(122)
Comprehensive loss	$ (29,274)	$ (33,940)	$ (28,972)	$ (29,274)

See accompanying notes.

Trevi Therapeutics, Inc.

Consolidated Statements of Stockholders' Equity

(Amounts in thousands, except share amounts)

	Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance at December 31, 2020	18,546,786	$ 19	$ 174,240	$ —	$ (146,977)	$ 27,282
Stock-based compensation	—	—	2,543	—	—	2,543

Issuance of common stock from employee stock purchase plan	42,290	—	39	—	—	39
Issuance of common stock under the at-the-market sales agreement, net of commissions and allocated fees	2,895,518	3	7,092	—	—	7,095
Issuance of common stock to Lincoln Park Capital Fund (see Note 9)	170,088	—	375	—	—	375
Issuance of common stock and warrants under private placements, less issuance costs	4,225,053	4	13,674	—	—	13,678
Issuance of common stock from warrant exercise	2,626,069	3	—	—	—	3
Net loss	—	—	—	—	(33,940)	(33,940)
Balance at December 31, 2021	28,505,804	$ 29	$ 197,963	$ —	$ (180,917)	$ 17,075
Stock-based compensation	—	—	2,327	—	—	2,327
Issuance of common stock from exercise of stock options	51,005	—	139	—	—	139
Issuance of common stock under the at-the-market sales agreement, net of commissions and allocated fees	—	—	(42)	—	—	(42)
Issuance of common stock from Employee Stock Purchase Plan	54,457	—	56	—	—	56
Issuance of common stock and warrants under public offering and private placement, less issuance costs	20,433,624	20	105,375	—	—	105,395
Issuance of common stock from warrant exercise	10,898,540	11	11,772	—	—	11,783
Unrealized losses on available-for-sale marketable securities	—	—	—	(122)	—	(122)
Net loss	—	—	—	—	(29,152)	(29,152)
Balance at December 31, 2022	59,943,430	$ 60	$ 317,590	$ (122)	$ (210,069)	$ 107,459

	Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				

Balance at December 31, 2021	28,505,804	$ 29	$ 197,963	$ —	$ (180,917)	$ 17,075
Stock-based compensation	—	—	2,327	—	—	2,327
Issuance of common stock from exercise of stock options	51,005	—	139	—	—	139
Issuance of common stock from Employee Stock Purchase Plan	54,457	—	56	—	—	56
Issuance of common stock under the at-the-market sales agreement, net of commissions and allocated fees	—	—	(42)	—	—	(42)
Issuance of common stock and warrants under public offering and private placement, less issuance costs	20,433,624	20	105,375	—	—	105,395
Issuance of common stock from warrant exercise	10,898,540	11	11,772	—	—	11,783
Unrealized losses on available-for-sale marketable securities	—	—	—	(122)	—	(122)
Net loss	—	—	—	—	(29,152)	(29,152)
Balance at December 31, 2022	59,943,430	$ 60	$ 317,590	$ (122)	$ (210,069)	$ 107,459
Stock-based compensation	—	—	2,247	—	—	2,247
Issuance of common stock from exercise of stock options	146,081	—	74	—	—	74
Issuance of common stock from Employee Stock Purchase Plan	50,091	—	68	—	—	68
Issuance of common stock under the at-the-market sales agreement, net of commissions and allocated fees	750,000	1	1,670	—	—	1,671
Issuance of common stock from pre-funded warrant exercise	7,394,097	7	(7)	—	—	—
Unrealized gains on available-for-sale marketable securities	—	—	—	93	—	93
Net loss	—	—	—	—	(29,065)	(29,065)
Balance at December 31, 2023	68,283,699	$ 68	$ 321,642	$ (29)	$ (239,134)	$ 82,547

See accompanying notes.

Trevi Therapeutics, Inc.

Consolidated Statements of Cash Flows

(Amounts in thousands)

Year Ended December 31,	**Year Ended December 31,**

	2022	2021	2023	2022
Operating activities:				
Net loss	($ (29,152)	($ (33,940)	$ (29,065)	$ (29,152)
Adjustments to reconcile net loss to net cash used in operating activities:				
Depreciation	43	50		
Stock-based compensation			2,247	2,327
Write off of deferred offering costs			390	—
Operating lease right-of-use assets			377	—
Accretion/accrual of term loan discounts and debt issuance costs			180	520
Depreciation and amortization			123	43
Loss on disposal of property, equipment and leasehold improvements			10	—
Accretion of available-for-sale marketable securities, net	(829)	—	(2,125)	(829)
Change in fair value of term loan derivative liability	147	(82)	—	147
Accretion/accrual of term loan discounts and debt issuance costs	520	599		
Other expense related to transaction with Lincoln Park Capital Fund, LLC	—	375		
Stock-based compensation	2,327	2,543		
Changes in operating assets and liabilities:				
Prepaid expenses and other current assets	(601)	342	(2,850)	(601)
Accounts payable	9	831	(1,049)	9
Accrued expenses and other liabilities	(639)	336	52	(639)
Net cash used in operating activities	(28,175)	(28,946)	(31,710)	(28,175)
Investing activities:				
Proceeds from maturities of available-for-sale marketable securities	19,001	—	69,497	19,001
Purchases of available-for-sale marketable securities	(126,215)	—	(9,932)	(126,215)
Purchases of property, equipment and leasehold improvements	(159)	—	(137)	(159)

Net cash used in investing activities	(107,373)	—		
Net cash provided by (used in) investing activities			59,428	(107,373)
Financing activities:				
Repayments of term loan	(5,833)	—		
Payments of financing costs of term loan	(21)	(68)		
Proceeds from sale of common stock and warrants under public offering and private placement, net of issuance costs	105,410	13,678		
Proceeds from exercises of warrants	11,782	3		
Proceeds from at-the-market sales, net of commissions			1,710	—
Proceeds from exercises of stock options	139	—	74	139
Proceeds from employee stock purchase plan	56	39	68	56
Proceeds from at-the-market sales, net of commissions	—	7,505		
Repayments of term loan, term loan final fee and prepayment premium			(9,409)	(5,833)
Payments of offering costs	(226)	(382)	(258)	(226)
Net cash provided by financing activities	111,307	20,775		
Net decrease in cash and cash equivalents	(24,241)	(8,171)		
Payments of finance lease			(95)	—
Proceeds from sale of common stock and warrants in public offering and private placement, net of issuance costs			—	105,410
Proceeds from exercises of warrants			—	11,782
Payments of financing costs of term loan			—	(21)
Net cash (used in) provided by financing activities			(7,910)	111,307
Net increase (decrease) in cash and cash equivalents			19,808	(24,241)
Cash and cash equivalents at beginning of period	36,830	45,001	12,589	36,830
Cash and cash equivalents at end of period	12,589	36,830		
	$ 89	$ 30	$ 32,397	$ 12,589

Supplemental disclosure of cash flow information:				
Interest paid	$ 594	$ 603	$ (331)	$ (594)
State research tax credits exchanged for cash	$ —	$ 18	$ 55	$ —
Supplemental disclosure of non-cash financing activities:				
Offering costs included in accrued expenses	$ 15	$ 41	$ —	$ 15

See accompanying notes.

Trevi Therapeutics, Inc.

Notes to Consolidated Financial Statements

(Amounts in thousands, except share and per share amounts)

1. Nature of the Business

Trevi Therapeutics, Inc. (“Trevi” or the “Company”) is a clinical-stage biopharmaceutical company focused on the development and commercialization of the investigational therapy Haduvio (oral nalbuphine ER) for the treatment of chronic cough in adults with idiopathic pulmonary fibrosis (“IPF”) and other refractory chronic cough indications, and for the treatment of prurigo nodularis. cough. These conditions share a common pathophysiology that is mediated through opioid receptors in the central and peripheral nervous systems. Due to nalbuphine’s mechanism of action as a modulator of opioid receptors, the Company believes Haduvio has the potential to be effective in treating each of these conditions.

Haduvio is an oral extended-release formulation of nalbuphine. Nalbuphine is a mixed κ-opioid receptor agonist and μ-opioid receptor antagonist that has been approved and marketed as an injectable for pain indications for more than 20 years in the United States (“U.S.”) and Europe. The κ- and μ-opioid receptors are known to be critical mediators of cough and itch. Nalbuphine’s mechanism of action also mitigates the risk of abuse associated with μ-opioid agonists because it antagonizes or blocks, the μ-opioid receptor. Parenteral nalbuphine is not scheduled as a controlled substance in the U.S. and most of Europe.

The Company’s Consolidated Financial Statements have been prepared on the basis of continuity of operations, realization of assets and the satisfaction of liabilities and commitments in the ordinary course of business. The Company has financed its operations to date primarily through private placements of its redeemable convertible preferred stock and convertible notes prior to its initial public offering (“IPO”), borrowings under its prior term loan facility, proceeds from its IPO and concurrent private placement completed in May 2019, sales of its common stock pursuant to the at-the-market Sales Agreement (the “ATM Sales Agreement”) (Note 9) with SVB Securities LLC (formerly SVB Leerink LLC) (“SVB Securities”)

that the Company entered into in June 2020, the term loan facility with Silicon Valley Bank ("SVB") that the Company entered into in August 2020 (Note 8), proceeds from the private placements completed in October 2021 and April 2022 (Note 9), proceeds from the exercise of common stock warrants that were issued in the October 2021 private placements and proceeds from the public offering completed in October 2022 (Note 9). The Company has incurred recurring losses since inception, including net losses of $29.2 29.1 million and $33.9 29.2 million for the years ended December 31, 2022 December 31, 2023 and 2021, 2022, respectively. As of December 31, 2022 December 31, 2023, the Company had cash, cash equivalents and marketable securities of $120.5 83.0 million compared to $36.8 120.5 million of cash, and cash equivalents and marketable securities as of December 31, 2021 December 31, 2022. The Company had incurred losses and negative cash flows from operations and had an accumulated deficit of $210.1 239.1 million as of December 31, 2022 December 31, 2023. The Company expects to continue to incur losses for the foreseeable future. As of March 16, 2023 March 20, 2024, the date of issuance of these Consolidated Financial Statements, the Company believes that its cash, cash equivalents and marketable securities as of December 31, 2022 December 31, 2023, will be sufficient to fund its operating expenses and capital expenditure requirements for 12 months from the date of issuance of these Consolidated Financial Statements.

2. Summary of Significant Accounting Policies

Basis of Presentation

The accompanying Consolidated Financial Statements include the accounts of Trevi Therapeutics, Inc. and its wholly-owned subsidiary Trevi Therapeutics Limited. Intercompany balances and transactions have been eliminated.

All amounts presented are in thousands of dollars, except share and per share amounts, unless noted otherwise. The Company has evaluated events occurring subsequent to December 31, 2022 December 31, 2023 for potential recognition or disclosure in the Consolidated Financial Statements and concluded there were no subsequent events that required recognition or disclosure.

Use of Estimates

The preparation of financial statements in conformity with accounting principles generally accepted in the U.S. ("GAAP") requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities at the date of the financial statements and the reported amounts of the expenses during the reporting periods. Significant estimates and assumptions reflected in these Consolidated Financial Statements include but are not limited to the recognition of research and development ("R&D") expenses, the valuation of stock-based awards and the valuation allowance of deferred tax assets resulting from net operating losses. assets. In addition, management's assessment of the Company's ability to continue as a going concern involves the estimation of the amount and timing of future cash inflows and outflows. Changes in estimates are recorded in the period in which they become known. Actual results could differ from those estimates.

Cash Equivalents

The Company classifies short-term, highly liquid investments with an original term of three months or less at the date of purchase as cash equivalents.

Marketable Securities

The Company generally invests its excess cash in money market funds and investment grade short- to intermediate-term fixed income securities. Such investments are included in cash and cash equivalents or marketable securities on the Consolidated Balance Sheet. Marketable securities with an original maturity date greater than 90 days at each balance sheet date are classified as short-term. Marketable securities are classified as current assets as these investments are intended to be available to the Company for use in funding current operations. All of the Company's marketable securities are considered available-for-sale and are reported at fair value value. For securities with unrealized gains and losses, when the Company expects to receive cash flows sufficient to recover the amortized cost basis of a security, such gains and losses are included in accumulated other comprehensive income as a component of stockholders' equity. Credit losses are identified when the Company does not expect to receive cash flows sufficient to recover the amortized cost basis of a security. In the event of a credit loss, only the amount associated with the credit loss is recognized in interest income, net on the Consolidated Statements of Comprehensive Loss. The amortized cost of debt securities is adjusted for amortization of premiums and accretion of discounts to maturity, which is included in interest income, net on the Consolidated Statements of Comprehensive Loss. Realized gains and losses, and declines in value judged to be other-than-temporary, if any, on marketable securities are included in interest income, net on the Consolidated Statements of Comprehensive Loss. The cost of securities sold is determined using specific identification.

The Company evaluates whether declines in the fair values of its marketable securities below their amortized cost are other-than temporary credit losses on a quarterly basis. This evaluation consists of several qualitative and quantitative factors regarding the severity and duration of the unrealized loss, as well as the Company's ability and intent to hold the marketable security until a forecasted recovery occurs. Additionally, the Company assesses whether it has plans to sell the marketable security or whether it is more likely than not that it will be required to sell any marketable securities before recovery of its amortized cost basis. Factors considered include quoted market prices, recent financial results and operating trends, implied values from any recent transactions or offers of investee securities, credit quality of debt instrument issuers, other publicly available information that may affect the value of the marketable security, duration and severity of the decline in value, and the Company's strategy and intentions for holding the marketable security.

Fair Value Measurements

The Company's financial instruments have consisted of cash and cash equivalents, available-for-sale marketable securities, other current assets, accounts payable, accrued expenses, term loans term loan derivative liability and warrants to acquire the Company's common stock. Fair value estimates of these instruments are made at a specific point in time,

based on relevant market information. The carrying amounts of cash and cash equivalents, other current assets, accounts payable and accrued expenses are generally considered to be representative of their respective fair values because of the short-term nature of those instruments. Available-for-sale marketable securities are reported at their fair values, based upon pricing of securities with the same or similar investment characteristics as provided by third-party pricing services, as described below. The carrying amount of the term loan approximates approximated its fair value due to its floating market-based interest rate. The fair value of the term loan derivative liability is was estimated utilizing a probability-weighted cash flow approach. The warrants to acquire the Company's common stock are not required to be accounted for at fair value.

Current accounting guidance defines fair value, establishes a framework for measuring fair value in accordance with Accounting Standards Codification ("ASC") 820, *Fair Value Measurements and Disclosures*, and requires certain disclosures about fair value measurements. The valuation techniques included in the guidance are based on observable and unobservable inputs. Observable inputs reflect readily obtainable data from independent sources, while unobservable inputs reflect market assumptions and are classified into the following fair value hierarchy:

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

Level 2—Observable inputs other than the quoted prices in active markets for identical assets and liabilities—such as quoted prices for similar instruments, quoted prices for identical or similar instruments in inactive markets, or other inputs that are observable or can be corroborated by observable market data.

Level 3—Unobservable inputs—includes amounts derived from valuation models where one or more significant inputs are unobservable and require the company to develop relevant assumptions.

Valuation Techniques - Level 2 Inputs

The Company estimates the fair values of its financial instruments categorized as level 2 in the fair value hierarchy, including U.S. Treasury securities, U.S. government agency obligations, corporate bonds, commercial paper, asset-backed securities and municipal bonds, by taking into consideration valuations obtained from third-party pricing services. The pricing services use industry standard valuation models, including both income- and market-based approaches, for which all significant inputs are observable, either directly or indirectly, to estimate fair value. These inputs include reported trades of and broker/dealer quotes on the same or similar securities, benchmark yields, issuer credit spreads, benchmark securities, and other

observable inputs. The Company obtains a single price for each financial instrument and does not adjust the prices obtained from the pricing service.

Property, Equipment and Leasehold Improvements

Property, equipment and leasehold improvements (consisting of furniture, computer and office equipment and leasehold improvements) are stated at cost, net of accumulated depreciation. Depreciation is calculated using the straight-line method over the estimated useful lives of the respective assets (three years for computer equipment, five years for furniture and office equipment, and the shorter of the term of the lease or useful life for leasehold improvements).

Impairment of Long-Lived Assets

ASC 360, *Property, Plant, and Equipment,* addresses the financial accounting and reporting for impairment or disposal of long-lived assets. The Company reviews the recorded values of long-lived assets for impairment whenever events or changes in business circumstances indicate that the carrying amount of an asset or group of assets may not be fully recoverable. There was no impairment or disposal of long-lived assets during the years ended December 31, 2022 and 2021.

Foreign Currency Transactions

The Company, at times, contracts with vendors and consultants outside of the U.S., resulting in liabilities denominated in foreign currency. The transactions are recorded in U.S. dollars on the transaction dates and any currency fluctuation through the payment date is recorded as currency gains or losses in other income, net in the Consolidated Statements of Comprehensive Loss.

Deferred Offering Costs

The Company capitalizes certain legal, professional, accounting and other third-party fees that are directly associated with in-process equity financings as deferred offering costs until such financings are consummated. After consummation of an equity financing, these costs are recorded in stockholders' equity as a reduction of additional paid-in capital generated as a result of the financings. Should the planned equity financing no longer be considered probable of being consummated, the deferred offering costs are expensed immediately as a charge to operating general and administrative expenses. The deferred offering costs are included in Other current and non-current assets on the Consolidated Balance Sheets.

Research and Development (" ("R&D" &D") Expenses

All of the Company's R&D expenses consist of expenses incurred in connection with the development of Haduvio. These expenses include certain payroll and personnel expenses, including stock-based compensation, consulting costs, contract manufacturing costs and fees paid to contract research organizations ("CROs") to conduct certain R&D activities on the Company's behalf. The Company does not allocate its costs by each indication for which it is developing Haduvio, as a significant amount of the Company's development activities broadly support all indications. In addition, several of the Company's departments support the Company's Haduvio drug candidate development program and the Company does not

identify internal costs for each potential indication. The Company expenses both internal and external R&D expenses as they are incurred.

Accrued R&D Expenses

The Company has entered into agreements with CROs, contract manufacturing organizations ("CMOs") and other companies that provide services in connection with the Company's R&D activities. The Company's R&D accruals are estimated based on the level of services performed, progress of the studies, including the phase or completion of events and contracted costs. The estimated costs of R&D provided, but not yet invoiced, are included in accrued expenses on the Consolidated Balance Sheets. If the actual timing of the performance of services or the level of effort varies from the original estimates, the Company will adjust the accrual accordingly. Payments made to CROs, CMOs and other companies under these arrangements in advance of the performance of the related services are recorded as prepaid expenses or as other non-current assets, as applicable, and are recognized as expenses as the goods are delivered or the related services are performed.

Patent Costs

All patent-related costs in connection with filing and prosecuting patent applications are expensed to general and administrative expense as incurred, as recoverability of such expenditures is uncertain.

Warrants

The Company determines the accounting classification of warrants that are issued, as either liability or equity, by first assessing whether the warrants meet liability classification in accordance with ASC 480, *Distinguishing Liabilities from Equity* ("ASC 480"), and then in accordance with ASC 815, *Derivatives and Hedging* ("ASC 815"), depending on the specific terms of the warrant. Under ASC 480, warrants are considered liability classified if the warrants are mandatorily redeemable, obligate the issuer to settle the warrants or the underlying shares by paying cash or other assets, or must or may require settlement by issuing variable number of shares.

If the warrants do not meet liability classification under ASC 480, the Company assesses the requirements under ASC 815, which states that contracts that require or may require the issuer to settle the contract for cash are liabilities recorded at fair value, irrespective of the likelihood of the transaction occurring that triggers the net cash settlement feature. If the warrants do not require liability classification under ASC 815, in order to conclude equity classification, the Company assesses whether the warrants are indexed to its common stock and whether the warrants are classified as equity under ASC 815 or other applicable GAAP. After all relevant assessments are made, the Company concludes whether the warrants are classified as liability or equity. Liability classified warrants are required to be accounted for at fair value both on the date of issuance and on subsequent accounting period ending dates, with all changes in fair value after the issuance date recorded in the statements of comprehensive loss as a gain or loss. For equity classified warrants, no changes in fair value are recognized after the issuance date.

F-9

Stock-Based Compensation

The Company accounts for stock-based compensation arrangements with employees and non-employees for consultancy services in accordance with ASC 718, *Stock Compensation* (“ASC 718”). ASC 718 requires the recognition of compensation expense, using a fair-value based method, for costs related to all stock-based awards including stock options. The Company’s determination of the fair value of stock-based awards on the date of grant utilizes the Black-Scholes valuation model for stock options with time-based and performance-based vesting and is impacted by the price of its common stock as well as changes in assumptions regarding a number of subjective variables. These variables include the expected term that stock options will remain outstanding, expected common stock price volatility over the term of the stock options, risk-free interest rates and expected dividends.

Changes in the variables can materially affect the fair value and ultimately how much stock-based compensation expense is recognized. These inputs are subjective and generally require analysis and judgment to develop.

Expected Term—The expected term assumption represents the weighted average period that the stock-based awards are expected to be outstanding. The Company has elected to use the “simplified method” for estimating the expected term of its stock options, whereby the expected term equals the arithmetic average of the vesting term and the original contractual term of the stock option.

Expected Volatility—For all stock options granted to date, the volatility data was estimated based on a study of publicly traded industry peer companies. For purposes of identifying these peer companies, the Company considered the industry, stage of development, size and financial leverage of potential comparable companies.

Expected Dividend—The Black-Scholes valuation model calls for a single expected dividend yield as an input. The Company currently has no history or expectation of paying cash dividends on its common stock.

Risk-Free Interest Rate—The risk-free interest rate is based on the yield available on U.S. Treasury zero-coupon issues similar in duration to the expected term of the stock-based award.

The fair value is recognized over the period during which an optionee is required to provide services in exchange for the stock option, known as the requisite service period (usually the vesting period) on a straight-line basis. For performance-based vesting, the fair value is recognized when it is probable the performance conditions will be achieved. The Company reassesses the probability of achieving the performance conditions at each reporting date. Forfeitures are accounted for as they occur.

Income Taxes

The Company accounts for income taxes using the asset and liability method. Under this method, deferred tax assets and liabilities are determined based on differences between the financial reporting and tax bases of assets and liabilities and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. Deferred income tax assets are reduced, as necessary, by a valuation allowance when management determines it is more likely than not that some or all of the tax benefits will not be realized.

The Company applies the provisions of ASC 740, *Income Taxes* ("ASC 740"), which prescribes a comprehensive model for how a company should recognize, measure, present and disclose in its financial statements uncertain tax positions that the company has taken or expects to take on a tax return. These Consolidated Financial Statements reflect expected future tax consequences of such positions presuming the taxing authorities possess full knowledge of the position and all relevant facts. There are no material uncertainties regarding the tax positions that the Company has taken through December 31, 2022 December 31, 2023 and December 31, 2021 December 31, 2022. The Company does not have any interest or penalties accrued related to tax positions as it does not have any unrecognized tax benefits.

Leases

Under ASC 842, *Leases* ("ASC 842"), the Company determines if an arrangement is a lease at its inception. Leases are classified as either operating or finance, based on the Company's evaluation of certain criteria. If an operating a lease has a term greater than one year, the lease is recognized in the balance sheet as a right-of-use asset and an operating a lease liability at lease commencement. The Company elected the short-term lease practical expedient, therefore, if an operating a lease has a term less than one year, the Company will not recognize the lease on its balance sheet. The

operating right-of-use asset represents the Company's right of use to an underlying asset for the term of the lease and the operating lease liability represents the Company's obligation to make lease payments arising from the lease.

Operating lease right-of-use assets and operating lease liabilities are determined and recognized on the commencement date of the lease based on the present value of lease payments over the term of the lease. As If the Company's leases do not provide an implicit rate within the lease, the Company uses its incremental borrowing rate, based on information available at the commencement date of the lease to determine the present value of the lease payments.

Operating lease right-of-use assets and operating lease liabilities are determined and recognized on the commencement date of the lease based on the present value of lease payments over the term of the lease. For operating leases, rent expense is recognized on a straight-line basis over the term of the lease, and right-of-use assets are subsequently re-measured to reflect the effect of uneven lease payments.

For finance leases, right-of-use assets are amortized on a straight-line basis over the shorter of the lease term or the useful life of the underlying asset. Expenses for finance leases include the amortization of right-of-use assets, which is recorded as depreciation and amortization expense, and interest expense, which reflects interest accrued on the lease liability.

Basic and Diluted Net Loss per Common Share

Basic and diluted net loss per common share outstanding is determined by dividing net loss by the weighted average common shares outstanding during the period. Basic shares outstanding includes the weighted average effect of the Company's outstanding pre-funded warrants, the exercise of which requires little or no consideration for the delivery of shares of common stock.

For all periods presented, shares issuable upon exercise of stock options and warrants to purchase shares of common stock (other than pre-funded warrants) have been excluded from the calculation because their effects would be anti-dilutive. Therefore, the weighted average common shares used to calculate both basic and diluted net loss per share are the same for each of the periods presented.

Segments

The Company has one reporting segment which is also the Company's only operating segment. Management uses one measurement of profitability and does not segregate its business for internal reporting. All long-lived assets are maintained in the U.S.

Recently Adopted Accounting Pronouncements

There have been no new pronouncements adopted during the year ended December 31, 2022 December 31, 2023, which materially impacted the Company's Consolidated Financial Statements.

Recently Issued Accounting Pronouncements

In November 2023, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update ("ASU") 2023-07, *Segment Reporting (Topic 280): Improvements to Reportable Segment Disclosures*, which requires public entities to disclose information about their reportable segments' significant expenses and other segment items on an interim and annual basis. Public entities with a single reportable segment are required to apply the disclosure requirements in ASU 2023-07, as well as all existing segment disclosures and reconciliation requirements in ASC 280, *Segment Reporting*, on an interim and annual basis. ASU 2023-07 is effective for fiscal years beginning after December 15, 2023, and for interim periods within fiscal years beginning after December 15, 2024, with early adoption permitted. The Company is currently evaluating the impact of adopting ASU 2023-07.

There have been no new pronouncements In December 2023, the FASB issued during the year ended December 31, 2022 ASU 2023-09, *Improvements to Income Tax Disclosures*, which could requires entities to disclose disaggregated information about their effective tax rate reconciliation as well as expanded information on income taxes paid by jurisdiction. The disclosure requirements will be expected applied on a prospective basis, with the option to materially apply them

retrospectively. The standard is effective for fiscal years beginning after December 15, 2024, with early adoption permitted. The Company is currently evaluating the impact the Company's Consolidated Financial Statements. of adopting ASU 2023-09.

3. Marketable Securities

The fair value and amortized cost of available-for-sale marketable securities by major security type as of December 31, 2022 are presented in the following table tables as of the periods presented (in thousands):

	December 31, 2022			
Type of Security	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
U.S. treasury securities	$ 9,914	$ —	$ (62)	$ 9,852
Asset backed securities	1,912	2	—	1,914
U.S. government agency securities	2,905	2	(4)	2,903
Corporate bonds	62,573	83	(143)	62,513
Commercial paper	30,739	—	—	30,739
Total marketable securities	$ 108,043	$ 87	$ (209)	$ 107,921

	December 31, 2023			
Type of security	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Corporate bonds	$ 45,686	$ 20	$ (53)	$ 45,653
U.S. government agency securities	4,917	9	(5)	4,921
Total marketable securities	$ 50,603	$ 29	$ (58)	$ 50,574

	December 31, 2022

Type of Security	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Corporate bonds	$ 62,573	$ 83	$ (143)	$ 62,513
Commercial paper	30,739	—	—	30,739
U.S. treasury securities	9,914	—	(62)	9,852
U.S. government agency securities	2,905	2	(4)	2,903
Asset backed securities	1,912	2	—	1,914
Total marketable securities	$ 108,043	$ 87	$ (209)	$ 107,921

The net amortized cost and fair value of available-for-sale marketable securities at December 31, 2022 are shown below presented in the following table (in thousands) as of the period presented by contractual maturity. Actual maturities may differ from contractual maturities because securities may be restructured, called or prepaid, or the Company intends may intend to sell a security prior to maturity.

	December 31, 2022		December 31, 2023	
	Amortized Cost	Fair Value	Amortized Cost	Fair Value
Due to mature:				
Less than one year	$ 69,527	$ 69,367	$ 49,651	$ 49,618
One year through two years	38,516	38,554	952	956
Total	$ 108,043	$ 107,921	$ 50,603	$ 50,574

	December 31, 2022	
	Amortized Cost	Fair Value
Due to mature:		
Less than one year	$ 69,527	$ 69,367
One year through two years	38,516	38,554
Total	$ 108,043	$ 107,921

During the year years ended December 31, 2022, December 31, 2023 and 2022, there have been were no realized gains or losses on available-for-sale marketable securities.

During As of the year years ended December 31, 2022, December 31, 2023 and 2022, no marketable securities had been in a continuous unrealized loss position for more than 12 months and the Company considered the loss to be temporary in nature. The Company reviewed the securities in the table above and considered the decline in market value for these securities to be primarily attributable to economic and market conditions. As of the periods noted in the table above, the Company did not intend to sell these securities and did not believe it was more likely than not that it would be required to sell these securities before recovery of their amortized cost basis. Accordingly, the Company did not recognize any other-than-temporary impairment credit losses on related to its marketable securities. securities in an unrealized loss position.

4. Fair Value Measurements

The following table summarizes the Company's financial assets and financial liabilities measured at fair value on a recurring basis as of December 31, 2022 and December 31, 2021, and the basis for that measurement, by level within the fair value hierarchy: hierarchy as follows (in thousands):

		Fair Value Measurement Using:					Fair Value Measurement Using:			
Balance Sheet Classification	**Type of Instrument**	**Level 1**	**Level 2**	**Level 3**	**Total**	**Type of Instrument**	**Level 1**	**Level 2**	**Level 3**	**Total**
December 31, 2022										
December 31, 2023										
Financial assets:										
Cash equivalents	Money market funds	1,158			1,158	Money market funds	$ 30,404	$ —	$ —	$ 30,404
		$ 9,852	$ —	$ —	$ 9,852					
Marketable securities	U.S. treasury securities		45,653		45,653	Corporate bonds	—	45,653	—	45,653
		—	—	—	—					
Marketable securities	Asset backed securities		1,919		1,919	U.S. government agency securities	—	4,921	—	4,921
		—	4,921	—	4,921					

Marketable securities	U.S. government agency securities	—	2,909	—	2,909				
Marketable securities	Corporate bonds	—	2,315	—	2,315				
Marketable securities	Commercial paper	—	309	—	309				
Total assets		$ 1,241	$ 8,409	$ —	$ 9,650	$ 30,404	$ 50,574	$ —	$ 80,978

Balance Sheet Classification	Type of Instrument	Fair Value Measurement Using: Level 1	Level 2	Level 3	Total
December 31, 2021					
Financial assets:					
Cash equivalents	Money market funds	$ 35,835	$ —	$ —	$ 35,835
Total assets		$ 35,835	$ —	$ —	$ 35,835
Financial liabilities:					
Term loan derivative liability		$ —	$ —	$ 114	$ 114
Total liabilities		$ —	$ —	$ 114	$ 114

Balance Sheet Classification	Type of Instrument	Fair Value Measurement Using: Level 1	Level 2	Level 3	Total
December 31, 2022					
Financial assets:					
Cash equivalents	Money market funds	$ 11,589	$ —	$ —	$ 11,589
Marketable securities	Corporate bonds	—	62,513	—	62,513
Marketable securities	Commercial paper	—	30,739	—	30,739
Marketable securities	U.S. treasury securities	9,852	—	—	9,852
Marketable securities	U.S. government agency securities	—	2,903	—	2,903
Marketable securities	Asset backed securities	—	1,914	—	1,914
Total assets		$ 21,441	$ 98,069	$ —	$ 119,510

The following table represents a roll-forward of the fair value of Level 3 instruments (significant unobservable inputs) (in thousands):

	December 31, 2022	2021	December 31, 2022
Financial liabilities			
Balance at beginning of period	$ 114	$ 196	$ 114
Change in fair value of term loan derivative liability	147	(82)	147
Net settlements	(261)	—	
Net settlements (see Note 8)			(261)
Balance at end of period	$ —	$ 114	$ —

5. Leases

The Company entered into a lease for office space in New Haven, CT, Connecticut, effective March 1, 2013, and entered into a First Amendment (the “First Amendment”) to such lease on December 5, 2017 and a Second Amendment (the “Second Amendment”) to such lease on November 21, 2022 (collectively, the “Office Space Lease”). The leased space approximates approximated 5,600 square feet and, prior to the Second Amendment, the Office Space Lease had a term of 60 months expiring on February 28, 2023. Under the First Amendment, the Company was required to make monthly payments ranging from approximately $10 to $12 through February 1, 2023 and provided for received two designated months of free rent. As a result of the Company entering into the Second Amendment, the leased space will

increase increased to 12,500 square feet effective in March 2023 and the term for the Office Space Lease was extended for an additional 60 months from its prior termination date, until February 28, 2028. The Second Amendment to the Office Space Lease requires monthly payments ranging from approximately $23 to $32 effective in March 2023 when the lease space is available for use, and through February 2028 and includes a tenant improvement allowance of approximately $670. The Second Amendment first year of payments are based on 10,500 square feet of occupied space, was not available as the second year of December 31, 2022 payments are based on 11,500 square feet of occupied space and therefore the Company has remaining lease payments are based on no 12,500t recorded a related right-of-use asset or operating lease liability. square feet of occupied space.

In December 2022, the Company entered into a 24 month lease for the financing of the furniture that will be installed as part of in the Company's Company's new office space. The furniture lease requires monthly payments of approximately $11 once the

furniture is delivered, which is estimated to occur starting in March 2023. The furniture had not been received as of December 31, 2022 and therefore the Company has not recorded a related right-of-use asset or lease liability. The Company also entered into an immaterial office equipment lease during the three months ended June 30, 2022 2022 that has a term of 36 months.

The incremental borrowing rate used on the First Amendment to the Office Space Lease was 13.0%. The right-of-use asset also includes any lease payments related to initial direct costs and prepayments and excludes lease incentives. Lease expense is recognized on a straight-line basis over the lease term. The Company had no significant new leases, except for the Second Amendment to the Office Space Lease, during the years ended December 31, 2022 and 2021.

The First Amendment to the Office Space Lease was an operating lease and the remaining term as of December 31, 2022 was less than one year. The Company has no financing leases. The following table summarizes presents the Company's operating leases lease-related assets and liabilities as presented on its Consolidated Balance Sheets: Sheets (in thousands):

	Classification on the Condensed Consolidated Balance Sheet	December 31, 2023	December 31, 2022
Assets:			
Operating lease assets	Operating lease right-of-use assets	$ 1,137	$ 24
Finance lease assets	Finance lease right-of-use assets	206	—
Total lease assets		$ 1,343	$ 24
Liabilities:			
Current			
Operating lease liabilities	Operating lease liabilities, current portion	$ 184	$ 25
Finance lease liabilities	Finance lease liabilities, current portion	122	—

Non-current			
Operating lease liabilities	Operating lease liabilities, non-current portion	1,001	2
Finance lease liabilities	Finance lease liabilities, non-current portion	31	—
Total lease liabilities		$ 1,338	$ 27

	December 31, 2022	December 31, 2021
Assets:		
Operating lease right-of-use asset	$ 24	$ 131
Liabilities:		
Operating lease liabilities, current portion	25	120
Operating lease liabilities, long term portion	2	24
Total operating lease liabilities	$ 27	$ 144

The following table presents information related to the Company's lease expense for the periods shown (in thousands):

	Year Ended December 31,	
	2023	2022
Operating lease expense	$ 287	$ 123
Finance lease expense	36	—
Total lease expense	$ 323	$ 123

Future minimum lease payments from December 31, 2022 December 31, 2023 until the expiration of the operating lease leases are as follows: follows (in thousands):

2023	$ 25
2024	2
2025	1
2026	—
Total lease payments	28

Less: imputed discount rate	(1)
Carrying value of operating lease liabilities	$ 27

	Operating Leases	Finance Leases
2024	$ 303	$ 126
2025	349	32
2026	368	—
2027	377	—
2028	95	—
Total minimum lease payments	1,492	158
Less: Amount of lease payments representing interest	(307)	(5)
Present value of future minimum lease payments	$ 1,185	$ 153

Lease expense under operating leases, including leases of office equipment, was $

123The following table presents certain information related to the lease terms and $120discount rates for the years ended December 31, 2022 and 2021, respectively. Lease payments made were $Company's leases (in thousands):130

	December 31,	
	2023	2022
Weighted average remaining lease term:		
Operating leases	4.3 years	0.3 years
Finance leases	1.3 years	not applicable
Weighted average discount rate:		
Operating leases	11.00%	13.00%
Finance leases	4.37%	not applicable

and $

139The following table presents supplemental cash flow information related to the Company’s leases for the periods shown (in thousands):

	Year Ended December 31,	
	2023	2022
Cash paid for amounts included in the measurement of lease liabilities:		
Operating cash outflows relating to operating leases	$ 231	$ 130
Finance lease payments	$ 95	$ —
Supplemental non-cash information:		

Right-of-use assets obtained in exchange for new operating lease liabilities	$ 1,289	$ 4
Right-of-use assets obtained in exchange for new finance lease liabilities	$ 242	$ —

in the years ended December 31, 2022 and 2021, respectively, with such amounts reflected in the Consolidated Statements of Cash Flows in operating activities.

6. Property, Equipment and Leasehold Improvements, Net

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

	December 31,		December 31,	
	2022	2021	2023	2022
Computer, website development and office equipment	$ 175	$ 45	$ 263	$ 175
Furniture and fixtures	37	60	41	37
Leasehold improvements	130	130	29	130
Construction in progress	53	—	17	53
	395	235	350	395
Less: Accumulated depreciation	(225)	(182)		
Less: Accumulated depreciation and amortization			(134)	(225)
Total property, equipment and leasehold improvements, net	$ 170	$ 53	$ 216	$ 170

Depreciation was $43 81 and $50 43 for the years ended December 31, 2022 December 31, 2023 and 2021, 2022, respectively.

7. Accrued Expenses

Accrued expenses consist of the following: following (in thousands):

	December 31,		December 31,	
	2022	2021	2023	2022
Accrued compensation and benefits	$ 1,508	$ 1,250	$ 1,614	$ 1,508

Accrued R&D projects	1,130	2,303	1,579	1,130
Accrued consulting and professional fees			510	382
Accrued other	498	79	6	498
Accrued consulting and professional fees	382	176		
Total accrued expenses	$ 3,518	$ 3,808	$ 3,709	$ 3,518

8. Debt

Silicon Valley Bank Term Loan

On May 9, 2023, the Company paid the remaining amount due under the SVB Loan Agreement, resulting in the full extinguishment of the SVB Term Loan (as described below). The total payoff amount was $6.5 million, consisting of the remaining principal amount due of $5.2 million, the final payment fee of $1.2 million, and $0.1 million of accrued interest and prepayment premium.

On August 13, 2020 (the “Effective Date”), the Company entered into a loan and security agreement (the “SVB Loan Agreement”) with Silicon Valley Bank as lender (“SVB”), as lender, pursuant to which SVB provided a term loan to the Company in the original principal amount of $14.0 million (the “SVB Term Loan”). The SVB Term Loan bears bore interest at a floating rate per annum equal to the greater of (A) the prime rate plus 1.00% and (B) 4.25%. If SVB received evidence satisfactory to it that the Company had (i) received positive data for the Phase 2b/3 clinical trial of Haduvio sufficient to advance Haduvio into a second Phase 3 clinical trial for prurigo nodularis, and (ii) raised sufficient financing to fund such Phase 3 clinical trial and the Company’s operations, (together, the “Phase 3 Event”), the interest rate under the SVB Term Loan would have been adjusted to a floating rate equal to the greater of (A) the prime rate plus 3.00% and (B) 6.25% (see term loan derivative liability discussion below). Commencing on March 1, 2022 and on the first business day of each month thereafter, the Company was required to make monthly interest payments and to repay the SVB Term Loan in 24 consecutive installments of principal plus monthly payments of accrued interest. All outstanding principal and accrued and unpaid interest under the SVB Term Loan and all other outstanding obligations with respect to the SVB Term Loan are were due and payable in full on February 1, 2024. The SVB Loan Agreement permits permitted voluntary prepayment of all, but not less than all, of the SVB Term Loan, subject to a prepayment premium. Such prepayment premium would be have been 3.00% of the principal amount of the SVB Term Loan if prepaid prior to the first anniversary of the Effective Date, 2.00% of the principal amount of the SVB Term Loan if prepaid on or after the first anniversary of the Effective Date but prior to the second anniversary of the Effective Date, and 1.00% of the principal amount of the SVB Term Loan if prepaid on or after the second anniversary of the Effective Date but prior to February 1, 2024. Upon repayment in full of the SVB Term Loan, the Company will be was required to pay a final payment fee equal to $1.2 million. The SVB Term Loan and related obligations under the SVB Loan Agreement are were secured by substantially all of the Company’s properties, rights and assets, except for its intellectual property (which is was subject to a negative pledge under the SVB Loan Agreement).

On July 6, 2021, the Company and SVB entered into a First Amendment (the “Loan Amendment”) to the SVB Loan Agreement. The Loan Amendment modified the conditions under which the Company was required to cash collateralize all outstanding amounts owed to SVB under the SVB Loan Agreement. Under the Loan Amendment, if the Company failed to

receive positive data in its Phase 2b/3 PRISM trial or to raise by June 30, 2022 sufficient net proceeds from the sale of equity securities to finance its planned second Phase 3 clinical trial of Haduvio for prurigo nodularis and its ongoing operations (each a “Milestone Condition”), the Company would be have been required to deposit unrestricted and unencumbered cash equal to 100% of all outstanding amounts owed to SVB in a cash collateral account with SVB, which could be have been used by SVB to prepay the SVB Term Loan at any time. In addition, the Loan Amendment provided that if the Company failed to maintain at least $20.0 million in unrestricted and unencumbered cash in its accounts with SVB at any time prior to the satisfaction of all the Milestone Conditions (the "Minimum “Minimum Required Cash" Cash”), the Company would be have been required to cash collateralize all outstanding amounts owed to SVB under the SVB Loan Agreement. The Company would also have been required to cash collateralize all outstanding amounts owed to SVB under the SVB Loan Agreement if it did not raise at least $15.0 million in net proceeds from the sale of equity securities during the period from June 1, 2021 through October 31, 2021. The Company satisfied this equity funding condition through a combination of equity issuances under the Company’s ATM at-the-market sales agreement entered into with SVB Securities LLC (formerly SVB Leerink LLC) (“SVB Securities”) in June 2020 (the “ATM Sales Agreement Agreement”) and two private placements, which took place in October 2021 (see Note 9).

On April 6, 2022, the Company and SVB entered into a Third Amendment (the “Third Amendment”) to the SVB Loan Agreement. The Third Amendment principally modified the conditions under which the Company would be have been required to cash collateralize all outstanding amounts owed to SVB under the SVB Loan Agreement. Under the terms of the Third Amendment, if the Company raised $45.0 million in net proceeds from the sale of equity securities (the “2022 Equity Event”), the Company’s obligations to achieve the Milestone Conditions and maintain the Minimum Required Cash would terminate have terminated and the sole remaining trigger for cash collateralization would be have been if the Company did not receive positive final data by December 31, 2022 from either its Phase 2b/3 PRISM trial of Haduvio for prurigo nodularis or its Phase 2 CANAL

---

trial of Haduvio for the treatment of chronic cough in adults with IPF. In addition, the Third Amendment modified the interest rate on the principal amount outstanding under the SVB Loan Agreement. As a result of the Third Amendment, amounts outstanding under the SVB Loan Agreement accrue accrued interest at a floating per annum rate equal to (i) prior to the occurrence of the 2022 Equity Event, the greater of (A) the prime rate plus 1.00% and (B) 4.25%, and (ii) upon and after the occurrence of the 2022 Equity Event, the greater of (A) the prime rate plus 3.00% and (B) 6.25%. The closing of the April 2022 Private Placement, as discussed in Note 8 below, constituted the 2022 Equity Event and thereby terminated the

Company's obligations to achieve the Milestone Conditions and maintain the Minimum Required Cash. On August 3, 2022, SVB confirmed that the reported data from the Phase 2b/3 PRISM trial satisfied the requirement for positive final data and that the cash collateralization requirements of the SVB Loan Agreement were no longer in effect.

The SVB Loan Agreement contains contained customary representations, warranties, events of default and covenants. The occurrence and continuation of an event of default could cause have caused interest to be charged at the rate that is was otherwise applicable plus 5.00% (unless SVB elects selected to impose a smaller increase) and would provide have provided SVB with the right to accelerate all obligations under the SVB Loan Agreement and exercise remedies against the Company and the collateral securing the SVB Term Loan and other obligations under the SVB Loan Agreement, including foreclosure against assets securing the SVB Term Loan and other obligations under the SVB Loan Agreement, including the Company's cash. The SVB Loan Agreement also restricts restricted the payment of dividends on the Company's common stock.

In August 2020, in connection with the SVB Term Loan, the Company paid $57 in financing costs to a third-party, which were recorded as deferred charges and will be were amortized over the life of the SVB Term Loan using the effective interest method. In connection with the Loan Amendment, the Company paid $68 in financing costs to a third-party, which were recorded as deferred charges and will be were amortized over the remaining life of the SVB Term Loan using the effective interest method. In connection with the Third Amendment, the Company paid $21 in financing costs to a third-party, which were recorded as deferred charges and will be were amortized over the remaining life of the SVB Term Loan using the effective interest method. Amortization of these deferred financing charges totaled $68 and $40 for the years ended December 31, 2022 and 2021, respectively, and is included in interest expense in the Company's Consolidated Statements of Comprehensive Loss. The unamortized deferred charges at December 31, 2022 and 2021 totaled $29 and $76, respectively, and are included as a direct reduction of the carrying value of the term loan payable on the Company's Consolidated Balance Sheets.

In August 2020, in connection with the execution of the SVB Loan Agreement, the Company paid $27 in financing costs to SVB, which were recorded as loan discounts. These loan discounts are were included as a reduction in the balance of the term loan payable on the Company's Consolidated Balance Sheet Sheets and will be were accreted over the life of the SVB Term Loan using the effective interest method. Accretion of these loan discounts totaled $9 and $11 for the years ended December 31, 2022 and 2021, respectively and is included in interest expense in the Company's Consolidated Statements of Comprehensive Loss. At December 31, 2022 and 2021, the loan discount-financing costs unamortized balance was $3 and $12, respectively.

In connection with the SVB Loan Agreement, the Company is was obligated to pay a final payment fee of $1.2 million upon repayment in full of the SVB Term Loan. The final payment fee is being was accrued over the life of the SVB Term Loan using the effective interest method and is was included as an increase in the balance of the term loan payable on the Company's Consolidated Balance Sheets. Accrual of The Company paid this final payment fee totaled of $383 1.2 and $474 for million on May 9, 2023 in connection with the years ended December 31, 2022 and 2021, respectively, and is included payoff in interest expense in full of the Company's Consolidated Statements of Comprehensive Loss. At December 31, 2022 and 2021, $1,040 and $657 was accrued for the final payment fee, respectively.SVB Term Loan.

Prior to the Third Amendment, the SVB Loan Agreement provided that upon SVB receiving evidence satisfactory to it that the Company had (i) received positive data for the Phase 2b/3 PRISM trial sufficient to advance Haduvio into a second Phase 3 clinical trial for prurigo nodularis and (ii) raised sufficient financing to fund such Phase 3 clinical trial and the Company's operations, the interest rate on the SVB Term Loan would increase by 2.00% (the "Contingent Interest Rate Increase") as described above. The Contingent Interest Rate Increase represented a free-standing financial instrument. Accordingly, the Company accounted for the Contingent Interest Rate Increase as a derivative under ASC 815, *Derivatives and Hedging* and therefore, recorded a term loan derivative liability for the Contingent Interest Rate Increase at its fair value of $187 on the Effective Date of the SVB Loan Agreement. The Company adjusted this liability to fair value at each reporting date it remained outstanding, with such adjustments recorded as non-cash charges in other income (expense), net in the Company's Consolidated Statements of Comprehensive Loss. The term loan derivative liability was previously presented as a current liability on the Company's Consolidated Balance Sheets as of December 31, 2021. Sheets. Upon recording such term loan derivative liability, the Company also recorded an offsetting term loan discount – interest, to be that was amortized to interest expense in the Company's Consolidated Statements of Comprehensive Loss through the SVB Term Loan's maturity date using the effective interest method. Such amortization was $60 and $74 for the years ended December 31, 2022 and 2021, respectively. At December 31, 2022 and 2021, the balance of the term loan discount – interest was $24 and $84,

---

respectively, and is included as a reduction in the balance of the term loan payable on the Company's Consolidated Balance Sheets. Upon entering into the Third Amendment, the Contingent Interest Rate Increase became effective and the Company recorded an increase to the total fair value of the term loan derivative liability of $136 for the three months ended June 30, 2022. in 2022. The term loan derivative liability was then settled and reclassed reclassified to both current and non-current interest payable, which are were presented as accrued liabilities and other non-current liabilities on the Company's Consolidated Balance Sheet as Sheet.

During the year ended December 31, 2023, an immaterial effect from early extinguishment of December 31, 2022.

Fair values of debt was recorded in connection with the term loan derivative liability were estimated utilizing a probability-weighted cash flow approach, including variables for Company paying the timing of the Phase 3 Event and other probability estimates. For the fair value calculations of the term loan derivative liability at December 31, 2021, significant inputs included the Contingent Interest Rate Increase of 2.00%, a discount rate of 12.0% and remaining amounts due under

the SVB Term Loan maturity date Agreement, which was included in other income, net on the Company's Consolidated Statements of February 1, 2024. Comprehensive Loss.

As of December 31, 2022 December 31, 2023, the Company had no outstanding borrowings, and December 31, 2021 as of December 31, 2022, the Company had outstanding borrowings of $8.2 million, and $14.0 million, respectively, under the SVB Term Loan and the term loan payable balance as presented in the Company's Consolidated Balance Sheets as of December 31, 2022 and 2021 Sheet was comprised as shown below. below (in thousands).

	December 31,		December 31, 2022
	2022	2021	
Principal outstanding under term loan	$ 8,167	$ 14,000	$ 8,167
Term loan discount-interest	(24)	(84)	(24)
Term loan discount-unamortized deferred charges	(29)	(76)	(29)
Term loan discount-financing costs, net of accretion	(3)	(12)	(3)
Term loan-final payment fee	1,040	657	1,040
	9,151	14,485	9,151
Less current portion	7,000	5,833	7,000
Term loan payable, non-current	$ 2,151	$ 8,652	$ 2,151

Interest expense on the SVB Term Loan, which is comprised of interest payments, accretion and amortization of term loan discounts and the accrual of the final payment fee, is shown below for the years ended December 31, 2022 and 2021. (in thousands). As of December 31, 2022 and 2021, , the weighted average interest rate applicable to borrowings under the SVB Term Loan was 5.36% and 4.25%, respectively. .

	Year Ended December 31,		Year Ended December 31,	
	2022	2021	2023	2022
Interest payments	$ 643	$ 603	$ 202	$ 643
Accrual of the final payment fee	383	474	150	383
Accretion and amortization of term loan discounts	137	125	30	137
	$ 1,163	$ 1,202	$ 382	$ 1,163

9. Stockholders' Equity

Preferred Stock

As of December 31, 2022 December 31, 2023 and 2021, 2022, the Company's restated certificate of incorporation authorized the Company to issue 5,000,000 shares of preferred stock, with a par value of $0.001 per share.

Common Stock

As of December 31, 2022 December 31, 2023 and 2021, 2022, the Company's restated certificate of incorporation authorized the Company to issue 200,000,000 shares of common stock, with a par value of $0.001 per share.

T

As of December 31, 2022 and 2021, the he Company had reserved shares of common stock for future issuance as shown in the table below:

	December 31, 2022	December 31, 2021
Shares of common stock reserved for future issuance under the 2012 Stock Incentive Plan	602,231	665,720
Shares of common stock reserved for future issuance under the 2019 Stock Incentive Plan	4,553,202	3,400,489
Shares of common stock reserved for future issuance under the 2019 Employee Stock Purchase Plan	701,232	470,631
Shares to be issued upon exercise of common stock warrants and pre-funded warrants	48,330,707	20,602,244
Shares to be issued upon sales under the LPC Purchase Agreement	30,000,000	30,000,000
	84,187,372	55,139,084

	December 31,	
	2023	2022
Shares of common stock reserved for future issuance upon exercise of outstanding warrants and pre-funded warrants	40,931,506	48,330,707
Shares of common stock reserved for future issuance under the 2019 Stock Incentive Plan	6,549,183	4,553,202
Shares of common stock reserved for future issuance under the 2019 Employee Stock Purchase Plan	1,177,456	701,232
Shares of common stock reserved for future issuance under the 2012 Stock Incentive Plan	565,792	602,231
Shares to be issued upon sales under the LPC Purchase Agreement	—	30,000,000
	49,223,937	84,187,372

At-the-Market Offering

In June 2020, the Company entered into the ATM Sales Agreement with SVB Securities, under which the Company may was able to issue and sell shares of its common stock, from time to time, having an aggregate offering price of up to

$12.0 million. In May 2022, the Company and SVB Securities amended the ATM Sales Agreement to increase the maximum aggregate offering price of common stock that it was able to issue and sell from time to time under the ATM Sales Agreement by $50.0 million, from $12.0 million to up to $62.0 million.

Sales of common stock under the ATM Sales Agreement may were able to be made by any method that was deemed an “at-the-market” offering as defined in Rule 415(a)(4) under the Securities Act of 1933, as amended. The Company was not obligated to make any sales of its common stock under the ATM Sales Agreement. The Company began making sales pursuant to the ATM Sales Agreement in July 2020. As of August 15, 2023, the date of termination of the ATM Sales Agreement, the Company had issued and sold an aggregate of 4,333,394 shares of common stock for gross proceeds of $12.7 million pursuant to the ATM Sales Agreement, before deducting estimated commissions and allocated fees of $1.0 million.

In June 2023, the Company filed with the SEC a universal shelf registration statement on Form S-3 (the “Shelf Registration Statement”), which allows the Company to offer and sell up to $200.0 million of common stock, preferred stock, debt securities, units and/or warrants from time to time pursuant to one or more offerings at prices and terms to be determined at the time of sale. The Shelf Registration Statement was filed to replace the Company’s prior universal shelf registration statement on Form S-3 and was declared effective on August 15, 2023. Further, in June 2023, the Company entered into a 2023 ATM sales agreement with Leerink Partners, LLC (formerly SVB Securities) (the “2023 ATM Sales Agreement”), under which the Company may issue and sell shares of common stock, from time to time by any method that is deemed an “at-the-market” offering as defined in Rule 415(a)(4) under the Securities Act of 1933, as amended. The Company is not obligated to make any sales of its common stock under the 2023 ATM Sales Agreement. The Company began making filed a prospectus under the Shelf Registration Statement for the offer and sale of shares of the Company’s common stock having an aggregate offering price of up to $75.0 million pursuant to the 2023 ATM Sales Agreement. In accordance with the terms of the 2023 ATM Sales Agreement, the ATM Sales Agreement terminated upon effectiveness of the Shelf Registration Statement, at which point the Company was no longer able to issue and sell shares of its common stock under the ATM Sales Agreement. As of December 31, 2023, the Company had not made any sales pursuant to the 2023 ATM Sales Agreement in July 2020, and as of December 31, 2022, the Company had issued and sold an aggregate of 3,583,394 shares of common stock for gross proceeds of $11.0 million, before deducting estimated commissions and allocated fees of $0.8 million.

In May 2022, the Company amended the ATM Sales Agreement with SVB Securities to increase the maximum aggregate offering price of common stock that it may issue and sell from time to time under the ATM Sales Agreement by

$50.0 million, from $12.0 million to up to $62.0 million. Agreement.

Equity Purchase Agreement

On June 18, 2021, the Company entered into a common stock purchase agreement ("LPC Purchase Agreement") with Lincoln Park Capital Fund, LLC ("Lincoln Park"). The LPC Purchase Agreement provides provided that, subject to the terms and conditions therein, the Company has had the right, but not the obligation, to sell, at its discretion, to Lincoln Park up to $15.0 million of shares of common stock over a 24-month period commencing on July 23, 2021. In addition, under the LPC Purchase Agreement, the The Company issued 170,088 shares of common stock to Lincoln Park as consideration for Lincoln Park's commitment to purchase shares of the Company's common stock under the LPC Purchase Agreement. The purchase price per share As of the July 23, 2023, no shares had been sold will be based on the market prices prevailing immediately preceding the time of sale as computed under the LPC Purchase Agreement. to Lincoln Park has covenanted not to cause or engage in any manner whatsoever, any direct or indirect short selling or hedging of the Company's common stock. The agreement may be terminated by the Company at any time, at its sole discretion, without any additional cost or penalty. Under the terms of the October 2021 private placements described below, the Company agreed to not issue or sell additional shares under and the LPC Purchase Agreement on or prior to April 6, 2023.terminated by its terms.

Private Placements

On October 5, 2021, the Company issued and sold to an initial investor, in a private placement priced at-the-market under Nasdaq rules, (i) 2,373,201 shares of the Company's common stock and accompanying warrants to purchase an aggregate of 4,746,402 shares of the Company's common stock, and (ii) pre-funded warrants to purchase up to an aggregate of 4,926,069 shares of the Company's common stock and accompanying warrants to purchase an aggregate of 9,852,138 shares of the Company's common stock. Each share of the Company's common stock and accompanying common stock warrants were sold together at a combined price of $1.62, and each pre-funded warrant and accompanying common stock warrants were sold together at a combined price of $1.619, for gross proceeds of approximately $11.8 million. Each pre-funded warrant had an exercise price of $0.001 per share, became exercisable immediately upon issuance and was exercisable until exercised in full. Of the accompanying common stock warrants, warrants to purchase an aggregate of 7,299,270 shares will expire on April 5, 2025, and warrants to purchase an aggregate of 7,299,270 shares will expire on October 5, 2028. The accompanying common stock warrants have an exercise price of $1.37 per share and became exercisable immediately upon issuance.

On October 18, 2021, the Company issued and sold to New Enterprise Associates 16, L.P., an existing stockholder of the Company ("NEA") and related party, in a private placement, 1,851,852 shares of the Company's common stock and

accompanying warrants to purchase an aggregate of 3,703,704 shares of the Company's common stock. Each share of the Company's common stock and accompanying common stock warrants were sold together at a combined price of $1.62 for gross proceeds of approximately $3.0 million. Of the accompanying common stock warrants, warrants to purchase an aggregate of 1,851,852 shares of the Company's common stock will expire on April 18, 2025, and warrants to purchase an

aggregate of 1,851,852 shares of the Company's common stock will expire on October 18, 2028. The accompanying common stock warrants have an exercise price of $1.37 per share and became exercisable immediately upon issuance.

Total net proceeds from the two October 2021 private placements were $13.7 million, after deducting issuance costs of $1.1 million.

On April 6, 2022, the Company entered into a securities purchase agreement (the "Securities Purchase Agreement") with certain purchasers, pursuant to which the Company agreed to issue and sell to the purchasers, in a private placement priced at-the-market under Nasdaq rules, (i) 4,580,526 shares of the Company's common stock at a purchase price of $1.90 per share, and (ii) pre-funded warrants to purchase up to an aggregate of 24,379,673 shares of common stock at a purchase price of $1.899 per warrant (the "April 2022 Private Placement"). Each pre-funded warrant has an exercise price of $0.001 per share, is exercisable immediately and will be exercisable until the pre-funded warrant is exercised in full. The April 2022 Private Placement, which closed on April 11, 2022, resulted in gross proceeds to the Company of approximately $55.0 million. NEA, an existing stockholder of the Company and a related party, as well as an affiliate of NEA, participated in the offering.

Public Offering

On September 27, 2022, the Company issued and sold 14,252,670 shares of the Company's common stock and, in lieu of common stock to certain investors, pre-funded warrants to purchase 14,247,330 shares of common stock in a public offering (the "September 2022 Offering"), at a public offering price of $1.93 per share of common stock and $1.929 per pre-funded warrant pursuant to an underwriting agreement (the "Underwriting Agreement") with SVB Securities, Stifel, Nicolaus & Company, Incorporated and Oppenheimer & Co. Inc., as representatives of the several underwriters (the "Underwriters"). Each pre-funded warrant has an exercise price of $0.001 per share, is exercisable immediately and will be exercisable until the pre-funded warrant is exercised in full. Under the terms of the Underwriting Agreement, the Company agreed not to issue and sell additional shares until after November 21, 2022 except in certain circumstances, including the issuance and sale of additional shares pursuant to the Underwriting Agreement. Under the terms of the Underwriting Agreement, the Company granted the Underwriters an option (the "Option"), exercisable for 30 days, to purchase up to an additional 4,275,000 shares of common stock (the "Additional Shares"), at the public offering price of $1.93 per share. The Underwriters partially exercised the Option to purchase 1,600,428 Additional Shares, which shares were issued and sold on October 25, 2022. The September 2022 Offering, including the initial closing on September 27, 2022 and the Option closing on October 25, 2022, resulted in aggregate gross proceeds to the Company of approximately $58.1 million.

Warrants

Warrant activity, including activity related to pre-funded warrants, for the year ended December 31, 2022 is shown in the table below:

	Number of Pre-funded Warrant Shares	Number of Common Stock Warrant Shares	Total Number of Warrant Shares	Weighted Average Exercise Price	Weighted Average Contractual Term	Number of Pre-funded Warrant Shares	Number of Common Stock Warrant Shares	Total Number of Warrant Shares	Weighted Average Exercise Price	Weighted Average Contractual Term
Outstanding as of December 31, 2021	2,300,000	18,302,244	20,602,244	$ 2.10	4.5					
Issued	38,627,003	—	38,627,003	$ 1.00						
Outstanding as of December 31, 2022						38,627,003	9,703,704	48,330,707	$ 0.28	5.1
Exercised	(2,300,000)	(8,598,540)	(10,898,540)	$ 1.37		(7,399,201)	—	(7,399,201)	$ 0.001	
Outstanding as of December 31, 2022	38,627,003	9,703,704	48,330,707	$ 0.28	5.1					
Outstanding as of December 31, 2023						31,227,802	9,703,704	40,931,506	$ 0.33	4.1

As of March 31, 2022, all of the pre-funded warrants from the October 2021 private placements had been exercised at the exercise price of $0.001 per share. The pre-funded and common stock warrants are classified as equity in accordance with ASC 815 given that the pre-funded and common stock warrants are indexed to the Company's own shares of common stock and meet the requirements to be classified in permanent equity.

Stock-Based Awards

The 2012 Stock Incentive Plan (the "2012 Plan" Plan") was adopted by the Company's board of directors and stockholders. The 2012 Plan provides for the issuance of stock-based awards to the Company's employees, officers, directors, consultants and advisors. The Company's board of directors administers the 2012 Plan. In April 2019, the Company's board of directors adopted a resolution effective on May 7, 2019, that no further equity-based awards may be granted under the 2012 Plan.

In April 2019, the Company's board of directors adopted the 2019 Stock Incentive Plan (the "2019 Plan"), which became effective on May 7, 2019. The 2019 Plan provides for the grant of incentive stock options, non-statutory stock options, stock appreciation rights, restricted stock awards, restricted stock units and other stock-based awards. The Company's employees, officers, directors, consultants and advisors are eligible to receive awards under the 2019 Plan. The 2019 Plan is administered by the Company's board of directors.

The total number of shares of common stock that may be issued under the 2019 Plan and the 2012 Plan was 5,155,433 7,114,975 and 4,066,209 5,155,433 as of December 31, 2022 December 31, 2023 and 2021, 2022, respectively, of which 705,150 1,802,675 and 1,136,737 705,150 shares remained available for grant under the 2019 Plan, respectively. Awards may be made under the 2019 Plan for up to such number of shares of the Company's common stock as is equal to the sum of: i) 1,578,947 shares; plus ii) the number of shares (up to 1,157,894 shares) of the Company's common stock subject to outstanding awards under the 2012 Plan that expire, terminate or are otherwise cancelled, forfeited or repurchased by the Company at their original issuance price pursuant to a contractual repurchase right; plus iii) an annual increase to be added on the first day of each fiscal year, beginning with 2020 and continuing through 2029, equal to the least of (a) 2,105,623 shares of common stock, (b) 4% of

the number of outstanding shares of the Company's common stock on such date, and (c) an amount determined by the Company's board of directors. Effective January 1, 2022 January 1, 2023 and January 1, 2021 January 1, 2022,

respectively, the number of shares reserved for issuance under the 2019 Plan increased, pursuant to the terms of the 2019 Plan, by an additional 1,140,232 2,105,623 shares and 741,871 1,140,232 shares, equal to the 2019 Plan determined maximum and 4% of the Company's then-outstanding common stock. stock, respectively.

Options granted under the 2019 Plan and the 2012 Plan have a maximum term of ten years. Options granted to employees, officers and non-employees generally vest over four years based on varying vesting schedules that primarily include: 25% vesting on the first anniversary date of grant and the balance ratably over the next 36 months or vesting in equal monthly or quarterly installments over four years. Options granted to directors generally vest over one to two years. The Company generally settles stock option exercises with newly issued common shares. As of December 31, 2022 December 31, 2023 and 2021, 2022, respectively, options to purchase 3,848,052 4,746,508 and 2,263,752 3,848,052 shares of common stock were granted and outstanding, net of cancelations, cancellations, under the 2019 Plan. As of December 31, 2022 December 31, 2023 and 2021, 2022, respectively, options to purchase 602,231 565,792 and 665,720 602,231 shares of common stock were granted and outstanding, net of cancellations, under the 2012 Plan.

In February 2021, 2024, the compensation committee of the Company's board of directors approved the grant of Company granted 832,250 stock options to purchase 450,875 shares of common stock with performance-based vesting ("PSOs") to employees of the Company. The PSOs granted in February 2021, 2024 vest based on the timing and successful results of the Company's PRISM or CANAL clinical trials.

A summary of the Company's combined stock option activity for the 2019 Plan and the 2012 Plan for the year ended December 31, 2022 is as follows:

	Number of Option Shares	Weighted Average Exercise Price	Weighted Average Contractual Term	Aggregate Intrinsic Value
			(in years)	(in thousands)
Outstanding as of December 31, 2021	2,929,472	$ 4.51	7.6	$ —
Granted	1,669,250	$ 1.11		
Forfeited	(53,513)	$ 3.59		
Expired	(43,921)	$ 5.26		
Exercised	(51,005)	$ 2.73		
Outstanding as of December 31, 2022	4,450,283	$ 3.26	7.6	$ 1,672
Options exercisable as of December 31, 2022	2,196,428	$ 4.71	6.3	$ 65
Options unvested as of December 31, 2022	2,253,855	$ 1.84	8.9	$ 1,607

	Number of Option Shares	Weighted Average Exercise Price	Weighted Average Contractual Term	Aggregate Intrinsic Value
			(in years)	(in thousands)

Outstanding as of December 31, 2022	4,450,283	$ 3.26	7.6	$	1,672
Granted	1,563,500	$ 2.62			
Forfeited	(318,075)	$ 1.77			
Expired	(237,327)	$ 3.23			
Exercised	(146,081)	$ 0.51			
Outstanding as of December 31, 2023	5,312,300	$ 3.24	7.3	$	685
Options exercisable as of December 31, 2023	2,805,959	$ 4.16	6.0	$	273
Options unvested as of December 31, 2023	2,506,341	$ 2.20	8.8	$	412

The weighted average grant-date fair value per share of stock options granted was $0.93 2.24 and $2.28 0.93 for the years ended December 31, 2022 December 31, 2023 and 2021, 2022, respectively.

The aggregate fair value of stock options that vested during the years ended December 31, 2022 December 31, 2023 and 2021 2022 was $1.7 million and $2.9 million, and $2.4 million, respectively.

The aggregate intrinsic value of stock options is calculated as the difference between the exercise price of the stock options and the fair value of the Company's common stock for those stock options that had exercise prices lower than the fair value of the Company's common stock. The aggregate intrinsic value of stock options exercised during the year years ended December 31, 2022 December 31, 2023 and 2022 was $173 and $33. No stock options were exercised during the year ended December 31, 2021.

, respectively.

The range of assumptions that the Company used to determine the fair value of the stock options granted were as follows, presented on a weighted average basis: follows:

	Year Ended December 31,		Year Ended December 31,	
	2022	2021	2023	2022
Risk-free interest rate	2.4%	0.8%	3.4% - 4.8%	1.9% - 4.2%
Expected volatility	103.3%	94.0%	101.6% - 147.1%	101.7% - 108.6%
Expected dividend yield	—	—	—	—
Expected life of options (in years)	6.9	6.5		
Expected term (in years)			5.5 - 7.0	5.5 - 7.0

In April 2019, the Company's board of directors adopted the 2019 Employee Stock Purchase Plan (the "2019 ESPP"), which became effective on May 7, 2019. The 2019 ESPP is administered by the Company's board of directors.

The total number of shares of common stock that may be issued under the 2019 ESPP was 803,976 1,177,456 as of December 31, 2022, of which 701,232 shares remain available for issuance. December 31, 2023. The number of shares of the Company's common stock that have been approved to be issued under the 2019 ESPP is equal to the sum of i) 155,106 shares plus ii) an annual increase to be added on the first day of each fiscal year, beginning with the fiscal year ending December 31, 2020 and continuing for each fiscal year until and including, the fiscal year ending December 31, 2029, equal to the least of (a) 526,315 shares of common stock, (b) 1% of the number of

outstanding shares of the Company's common stock on such date and (c) an amount determined by the Company's board of directors. Effective January 1, 2022 January 1, 2023 and January 1, 2021 January 1, 2022, respectively, the aggregate number of shares of the Company's common stock that may be issued under the 2019 ESPP increased, pursuant to the terms of the 2019 ESPP, by an additional 285,058 526,315 shares and 185,467 285,058 shares, equal in each case to the lesser of the 2019 ESPP determined maximum and 1% of the Company's then-outstanding common stock.

The following table summarizes the classifications of stock-based compensation expenses for the 2012 Plan, the 2019 Plan and the 2019 ESPP recognized in the Consolidated Statements of Comprehensive Loss: Loss (in thousands):

	Year Ended December 31,		Year Ended December 31,	
	2022	2021	2023	2022
General and administrative expense	$ 1,512	$ 1,800	$ 1,376	$ 1,512
Research and development expense	815	743	871	815
	$ 2,327	$ 2,543	$ 2,247	$ 2,327

As of December 31, 2022 December 31, 2023, total unrecognized compensation cost related to the unvested share-based awards was $2.9 3.8 million, which is expected to be recognized over a weighted average period of 2.4 2.7years.

10. Income Taxes

During the years ended December 31, 2022 and 2021, the The Company recorded an income tax benefit related to state research and development tax credits of $ credits. 36 and $21, respectively.

The components of the income tax benefit for the years ended December 31, 2022 and 2021, periods shown are as follows: follows (in thousands):

	Year Ended December 31,

	2022	2021
Current:		
Federal	$ —	$ —
State	(36)	(21)
	(36)	(21)
Deferred:		
Federal	—	—
State	—	—
	—	—
Income tax benefit	$ (36)	$ (21)

	Year Ended December 31,	
	2023	2022
Current:		
Federal	$ —	$ —
State	(32)	(36)
	(32)	(36)
Deferred:		
Federal	—	—
State	—	—
	—	—
Income tax benefit	$ (32)	$ (36)

The following table provides a reconciliation between income tax benefit and the expected tax benefit at the statutory rate for the years ended December 31, 2022 and 2021:rate:

	Year Ended December 31,		Year Ended December 31,	
	2022	2021	2023	2022
Federal statutory income tax rate	21.0%	21.0%	21.0%	21.0%
State income tax benefit—net of federal tax	5.8	6.0	5.8	5.8
R&D tax credits			2.9	2.5
Refundable tax credit			0.1	0.1

Permanent adjustments			(0.6)	(0.6)
Change in valuation allowance	(28.7)	(29.1)	(29.1)	(28.7)
Refundable tax credit	0.1	0.1		
R&D tax credits	2.5	2.1		
Permanent adjustments	(0.6)	—		
Effective income tax rate	0.1%	0.1%	0.1%	0.1%

Significant components of the Company's deferred tax assets and liabilities are as follows:follows (in thousands):

	December 31,	
	2022	2021
Net operating loss carryforwards	$ 48,030	$ 45,693
Federal and state tax credits	5,569	4,801
Capitalized R&D	4,825	—
Other	2,868	2,237
Deferred tax assets	61,292	52,731
Other	(220)	(35)
Deferred tax liabilities	(220)	(35)
Valuation allowance	(61,072)	(52,696)
Net deferred tax asset	$ —	$ —

	December 31,	
	2023	2022
Net operating loss carryforwards	$ 50,305	$ 48,030
Capitalized R&D	9,662	4,825
Federal and state tax credits	6,440	5,569
Other	3,647	2,868

Deferred tax assets	70,054	61,292
Other	(552)	(220)
Deferred tax liabilities	(552)	(220)
Valuation allowance	(69,502)	(61,072)
Net deferred tax asset	$ —	$ —

For the years ended December 31, 2022 December 31, 2023 and 2021, 2022, the Company generated federal and state net operating losses (“NOLs”) of approximately $8.7 8.1 million and $32.1 8.7 million, respectively. At December 31, 2022 December 31, 2023 and 2021, 2022, the federal and state net operating loss balances were approximately $178.4 186.9 million and $169.7 178.7 million, respectively. The federal operating losses generated prior to 2018 will expire in years 2031 through 2037, unless previously utilized. The federal operating losses generated in 2018 or later can be carried forward indefinitely, however will only offset 80% of taxable income in a carryforward year. The state operating losses generated will expire in years 2031 through 2043, unless previously utilized. The Company also generated federal R&D tax credits for the years ended December 31, 2022 December 31, 2023 and 2021 2022 of approximately $756 848 and $702 756, respectively. At December 31, 2022 December 31, 2023 and 2021, 2022, the federal R&D tax credit carryforwards were approximately $5.4 6.2 million and $4.6 5.4 million, respectively. These credits will expire in years 2032 through 2042 2043, unless previously utilized. The Company completed a detailed Section 382 analysis, and due to multiple historical ownership changes, the Company's NOLs as of December 31, 2022, in the amount of $178.4 million and R&D tax credits in the amount of $5.4 million are subject to limitation. If a further ownership change occurs, the Company's ability to use its tax attributes might be further limited.

The Company also generated state research tax credits for the years ended December 31, 2022 December 31, 2023 and 2021 2022 of approximately $118 265 and $149 118, respectively. At December 31, 2023 and 2022, the state R&D tax credit carryforwards were approximately $275 and $244, respectively. The Company applied to exchange a portion of these credits for cash under a state-run program. These amounts, $36 32 and $21 36 for the years ended December 31, 2022 December 31, 2023 and 2021, 2022, respectively, were recognized as current income tax benefits in the Company’s Consolidated Statements of Comprehensive Loss. At each of December 31, 2022 December 31, 2023 and 2021, 2022, the Company’s Consolidated Balance Sheets reflect income tax receivables of $36 32 and $21 36 respectively, related to these credits. Because of the net operating loss and research credit carryforwards, tax years 2012 2013 through 2021 2022 remain open to U.S. federal and state tax examinations.

Beginning in 2022, the Tax Cuts and Jobs Act of 2017 ("TCJA") eliminated the option to deduct research and development expenditures in the current year and requires taxpayers to amortize U.S. expenses over five years and non-U.S. expenses over fifteen years pursuant to Internal Revenue Code Section 174. In the future, Congress may consider legislation that would defer the amortization requirement to later years, possibly with retroactive effect. In the meantime, we expect to continue to capitalize research and development expenses under the current tax law. The impact of Section 174 on the Company's deferred tax assets depends on the amount of research and development expenditures incurred by the

Company and whether the IRS issues guidance on the provision, which differs from the Company's current interpretation, among other things. For the year for the years ended December 31, 2022 December 31, 2023 and 2022 , this provision resulted in a deferred tax asset assets of $4,837 and $4,825. , respectively.

Income taxes are provided using the asset/liability method, in which deferred taxes are recognized for the tax consequences of temporary differences between the financial statement carrying amounts and tax bases of existing assets

and liabilities. The Company reviews deferred tax assets for recoverability on a regular basis. In assessing the need for a valuation allowance, the Company considers both positive and negative evidence related to the likelihood of realization of the deferred tax assets. The weight given to the positive and negative evidence is commensurate with the extent to which the evidence may be objectively verified. Accounting guidance states that a cumulative loss in recent years is a significant piece of negative evidence that is difficult to overcome in determining that a valuation allowance is not needed against deferred tax assets. As such, it is generally difficult for positive evidence regarding projected future taxable income exclusive of reversing taxable temporary differences to outweigh objective negative evidence of recent financial reporting losses.

The Company determined that operating losses it incurred since its inception on March 17, 2011, represented negative evidence sufficient to conclude a valuation allowance was necessary. As such, the Company has recorded a valuation allowance of $61.1 69.5 million and $52.7 61.1 million at December 31, 2022 December 31, 2023 and 2021, 2022, respectively, as a reserve against its net deferred tax assets. These balances reflect increases in the valuation allowance of $8.4 million in each of 2023 and $9.9 million in 2022, and 2021, respectively, both representing an increase in net deferred tax assets.

The Company applies the provisions of ASC 740, which prescribes a comprehensive model for how a company should recognize, measure, present, and disclose in its financial statements uncertain tax positions that the Company has taken or expects to take on a tax return. The financial statements reflect expected future tax consequences of such positions presuming the taxing authorities possess full knowledge of the position and all relevant facts. As a result of the implementation of ASC 740, the Company recognized no adjustment for unrecognized income tax benefits. The Company has not, as of yet, conducted a study of R&D tax credit carryforwards. Such a study could result in an adjustment to the Company’s R&D tax credit carryforwards; however, until a study is completed and any potential adjustment is known, no amounts are being presented as an uncertain tax position. A full valuation allowance has been provided against the

Company's R&D tax credits and, if an adjustment is required in the future, this adjustment would be offset by a corresponding adjustment to the valuation allowance. For the years ended December 31, 2022 December 31, 2023 and 2021, 2022, the Company had no unrecognized tax benefits or related interest and penalties accrued. In the event the Company determines that accrual of interest or penalties are necessary in the future, the amount will be presented as a component of interest expense.

11. Net Loss per Share

The following table summarizes the computation of basic and diluted net loss per share attributable to common stockholders of the Company: Company (in thousands, except share and per share amounts):

	Year Ended December 31,	
	2022	2021
Net loss	$ (29,152)	$ (33,940)
Weighted average common shares used in net loss per share attributable to common stockholders, basic and diluted	64,541,911	22,841,481
Basic and diluted net loss per common share outstanding	$ (0.45)	$ (1.49)

	Year Ended December 31,	
	2023	2022
Net loss	$ (29,065)	$ (29,152)
Weighted average common shares used in net loss per share attributable to common stockholders, basic and diluted	99,033,373	64,541,911
Basic and diluted net loss per common share outstanding	$ (0.29)	$ (0.45)

Basic shares outstanding includes the weighted average effect of the Company's pre-funded warrants from the date of issuance, the exercise of which requires little or no consideration for the delivery of shares of common stock. As of December 31, 2022, December 31, 2023 and 2022, the Company had pre-funded warrants to purchase 31,227,802 and 38,627,003 shares of common stock outstanding, respectively, which were issued in the April 2022 Private Placement and the September 2022 Offering, which warrants are included in the weighted average common shares used in calculating the net loss per share attributable to common stockholders, basic and diluted, for the year years ended December 31, 2022. December 31, 2023 and 2022.

The Company's potential dilutive securities, which include stock options and warrants that are not pre-funded, have been excluded from the computation of diluted net loss per share attributable to common stockholders whenever the effect of including them would be to reduce the net loss per share. In periods where there is a net loss, the weighted average number of common shares outstanding used to calculate both basic and diluted net loss per share attributable to common stockholders is the same. The following potential common shares, presented based on shares outstanding as of December 31, 2022 and 2021, respectively, were excluded from the calculation of diluted net loss per share attributable to common stockholders for the periods indicated because including them would have had an anti-dilutive effect:

Shares as of December 31,	Shares as of December 31,

	2022	2021	2023	2022
Warrants			9,703,704	9,703,704
Stock Options	4,450,283	2,929,472	5,312,300	4,450,283
Warrants	9,703,704	20,602,244		
	14,153,987	23,531,716	15,016,004	14,153,987

12. Collaborative and Licensing Agreements

The Company enters into collaborative and licensing agreements with pharmaceutical companies to in-license, develop, manufacture and/or market products that fit within its business strategy.

Endo Pharmaceuticals Inc.

In May 2011, the Company entered into an agreement with Penwest Pharmaceuticals Co., which subsequently merged into its parent, Endo Pharmaceuticals Inc. (“Endo”), for an exclusive worldwide sublicensable license under certain

patent rights and know-how controlled by Endo to develop and commercialize products incorporating nalbuphine hydrochloride in any formulation, including an extended-release formulation such as Haduvio, in all fields and for any use.

Under the license agreement, the Company paid Endo a non-creditable, non-refundable upfront license fee. The Company may also become obligated to make milestone payments to Endo of $0.3 million, which would become due upon the successful completion of the first Phase 3 clinical trial of a licensed product candidate, and $0.8 million, which would become due upon the marketing approval of a licensed product in the U.S. and to pay royalties based on net sales of the licensed products by the Company, its affiliates and sublicensees. In addition, the Company is obligated to pay Endo a low-to-mid double-digit percentage of certain income it receives from sublicensees, based on the date of the definitive agreement under which the sublicense was granted.

The Company’s royalty obligation with respect to each licensed product in each country commences upon the first commercial sale of the product in that country and extends until the later of the expiration, unenforceability or invalidation of the last valid claim of any licensed patent or application covering the licensed product in the country or the expiration of 10 years after the first commercial sale of the licensed product in the country, which period is referred to as the royalty term.

Upon the expiration of the royalty term for a product in a country, the Company is thereafter obligated to pay a low single-digit know-how and trademark royalty.

Under the agreement, the Company has granted Endo a non-exclusive, royalty-free (except for pass-through payments to third parties), sublicensable license under its relevant patent rights to use any improvement the Company makes to Endo's controlled release technology for any product other than the products under which it is licensed by Endo.

Both the Company and Endo have the right to terminate the agreement if the other party materially breaches the agreement and fails to cure the breach within specified cure periods. Endo also has the right to terminate in the event the Company undergoes specified bankruptcy, insolvency or liquidation events. The Company has the right to terminate the agreement at its convenience at any time on 180 days' notice to Endo. Additionally, if the Company or any of the Company's sublicensees challenge the validity or enforceability of any licensed patent rights covering a licensed product and that challenge is not terminated within a specified period, the agreement will immediately terminate and all licenses granted under the agreement shall be revoked.

Upon termination of the agreement, the Company must transfer to Endo all regulatory filings and approvals relating to the development, manufacture or commercialization of the licensed products and all trademarks, other than the Company's corporate trademarks, then being used in connection with the licensed products. If the agreement is terminated under certain specified circumstances, the Company will be deemed to have granted Endo a perpetual, royalty-free (except for pass-through payments to third parties), worldwide, exclusive, sublicensable license, under any improvements the Company made to the licensed know-how and any related patent rights the Company has, to manufacture and commercialize the licensed products.

13. Commitments and Contingencies

A significant portion of the Company's development activities are outsourced to third parties under agreements, including with CROs and contract manufacturers in connection with the production of clinical trial materials. These arrangements may require the Company to pay termination costs to the third parties for reimbursement of costs and expenses incurred in the event of the orderly termination of contractual services.

The Company also has commitments under lease and licensing agreements (Note 5 and Note 12).

14. Retirement Plan

In March 2013, the Company adopted and became a participating employer of a multiple employer defined contribution retirement plan that complies with Section 401(k) of the Code. All eligible employees of the Company are able to immediately participate in the plan (with an entry date of the first day of any month), with no minimum service requirement. The 401(k) plan provides that the Company make non-discretionary matching contributions of 50% of the first 6% of elective contributions. Participants are immediately vested in their contributions, as well as any earnings thereon. Vesting in the employer match contribution portion of their accounts, as well as any earnings thereon, is based on years of credited service, vesting over a four-year period, with 25% vesting per completed year. The Company's expense under the 401(k) plan, representing its employer matching contributions and additional contributions in accordance with regulatory compliance requirements, totaled $90 126 and $96 90 for the years ended December 31, 2022 December 31, 2023 and 2021, 2022, respectively.

Exhibit 10.11 4.2

0000950170-23-008472img131083460_0.jpg DESCRIPTION OF THE REGISTRANT'S SECURITIES REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES EXCHANGE ACT OF 1934

November 4, 2022

Dear David,

On behalf As of March 20, 2024, Trevi Therapeutics, Inc. ("we", "us" or the "Company") had one class of securities registered under Section 12 of the Securities Exchange Act of 1934, as amended (the "Company" or "Trevi" "Exchange Act"): our common stock, $0.001 par value per share.

The following description of our capital stock is intended as a summary only and therefore is not a complete description of our capital stock. This description is based upon, and is qualified by reference to, our restated certificate of incorporation, as amended (the "certificate of incorporation"), I am pleased our amended and restated bylaws (the "bylaws"), and applicable provisions of Delaware corporate law. You should read our certificate of incorporation and our bylaws, which are filed as exhibits to offer you employment with the Company Annual Report on Form 10-K of which this exhibit is a part, for the provisions that are important to you.

Authorized Capital Stock

Our authorized capital stock consists of 200,000,000 shares of common stock, par value $0.001 per share, and 5,000,000 shares of preferred stock, par value $0.001 per share.

Common Stock

Annual Meeting. Annual meetings of our stockholders are held on the following terms. date designated in accordance with our bylaws. Written notice must be given to each stockholder entitled to vote not less than 10 nor more than 60 days before the date of the meeting. The presence in person or by proxy of the holders of a majority in voting power of our issued and outstanding shares of capital stock entitled to vote at such meeting, present in person, present by means of remote communication in a manner, if any, authorized by the board of directors in its sole discretion, or represented by proxy, constitutes a quorum for the transaction of business at meetings of the stockholders. Special meetings of the stockholders may be called for any purpose by the board of directors. Except as may be otherwise provided by applicable law, our certificate of incorporation or our bylaws, all director elections shall be decided by a plurality of the votes cast by the stockholders entitled to vote on the election, and all other questions shall be decided by the holders of shares of stock having

a majority in voting power of the votes cast by the holders of all of the shares of stock present or represented at the meeting and voting affirmatively or negatively on such matter at a duly held meeting of stockholders at which a quorum is present.

Employment Voting Rights. You will Each holder of common stock is entitled to one vote for each share held of record on all matters to be hired voted upon by stockholders, including the election of directors. The common stock does not have cumulative voting rights.

Dividends. Subject to the rights, powers and preferences of any outstanding preferred stock, and except as provided by law or in our certificate of incorporation, dividends may be declared and paid or set aside for the position of Chief Medical Officer beginning on November 14, 2022(the "Start Date"), reporting to Jennifer Good, CEO. You will be responsible for performing the duties and responsibilities as are customarily associated with the position or as the Company may otherwise assign to you. Your primary place of employment will be home-based, with time spent in the New Haven, CT office or traveling for the Company. This time may vary based payment on the needs common stock out of funds lawfully available when and as declared by the Company, but is generally expected board of directors.

Liquidation, Dissolution and Winding Up. In the event of our liquidation, dissolution or winding up, the holders of our common stock are entitled to be about 20% receive all assets available for distribution to stockholders after the payment of your time. You agree to devote your full business time, best efforts, skill, knowledge, attention all debts and energies other liabilities and subject to the advancement prior rights of the Company's business any then outstanding preferred stock. The rights, preferences and interests and to the performance privileges of your duties and responsibilities as an employee holders of the Company, and shall not engage in any other employment, consulting or other business activity without the prior written consent of the CEO. In the course of your employment with the Company, you will be our common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of our preferred stock that we may designate and issue in the future.

Other Rights. Holders of the common stock have no right to:

- convert the stock into any other security;
- have the stock redeemed;
- purchase additional stock; or
- maintain their proportionate ownership interest.

There are no sinking fund provisions applicable to our common stock. Holders of shares of the common stock are not required to comply with, all Company policies make additional capital contributions.

Preferred Stock

We are authorized to issue "blank check" preferred stock, which may be issued in one or more series upon authorization of our board of directors. Our board of directors is authorized to fix the number of shares of such series of preferred stock and procedures such voting powers, full or limited, or no voting powers, and all such designations, preferences and relative, participating, optional or other special rights, and qualifications, limitations or restrictions of the shares of each series of preferred stock, including liquidation preferences,

dividend rights, conversion rights and redemption privileges. The authorized shares of our preferred stock are available for issuance without further action by our stockholders, unless such action is required by applicable laws law or the

---

rules of any stock exchange on which our securities may be listed. If the approval of our stockholders is not required for the issuance of shares of our preferred stock, our board may determine not to seek stockholder approval.

A series of our preferred stock could, depending on the terms of such series, impede the completion of a merger, tender offer or other takeover attempt. Our board of directors will make any determination to issue preferred shares based upon its judgment as to the best interests of our stockholders. Our directors, in so acting, could issue preferred stock having terms that could discourage an acquisition attempt through which an acquirer may be able to change the composition of our board of directors, including a tender offer or other transaction that some, or a majority, of our stockholders might believe to be in their best interests or in which stockholders might receive a premium for their stock over the then-current market price of the stock. There are no shares of preferred stock currently outstanding, and regulations. we have no present plans to issue any shares of preferred stock.

Provisions of Our Certificate of Incorporation and Bylaws and Delaware Law That May Have Anti-Takeover Effects

Base Salary Certain provisions of our certificate of incorporation and bylaws may have the effect of making it more difficult for a third party to acquire, or of discouraging a third party from attempting to acquire, control of us. Such provisions could limit the price that certain investors might be willing to pay in the future for shares of our common stock and may limit the ability of stockholders to remove current management or directors or approve transactions that stockholders may deem to be in their best interest and, therefore, could adversely affect the price of our common stock.

Board of Directors. During your employment, your base Our certificate of incorporation and bylaws provide for a board of directors divided as nearly equally as possible into three classes. Each class is elected to a term expiring at the annual salary will be $470,000, payable meeting of stockholders held in accordance with the regular payroll practices third year following the year of the Company and subject to applicable deductions and withholdings. Your salary may be adjusted such election. The number of directors comprising our board of directors is fixed from time to time in accordance with normal business practice and by the board of directors.

Removal of Directors by Stockholders. Delaware law provides that members of our board of directors may only be removed for cause by a vote of the holders of 75% of the outstanding shares entitled to vote on the election of the directors.

Stockholder Nomination of Directors. Our bylaws provide that, in the sole discretion case of an election of directors at an annual meeting, a stockholder must notify us in writing of any stockholder nomination of a director not more than 120 days and not less than 90 days prior to the first anniversary of the Company. preceding year's annual meeting; provided, that if the date of the annual meeting is advanced by more than 30 days or delayed by more than 60 days from such anniversary date, or if no annual meeting was held in the preceding year, notice by the stockholder to be timely must be so delivered not earlier than the 120th day prior to the date of such annual meeting and not later than the close of business on the later of (x) the 90th day prior to the date of such meeting and (y) the 10th day following the day on which notice of the date of such annual meeting was given or public disclosure of the date of such annual meeting was made, whichever occurs first. Our bylaws provide that, in the case of an election of directors at a special meeting, a stockholder must notify us in writing of any stockholder nomination of a director not earlier than the 120th day prior to such special meeting and not later than the close of business on the later of (x) the 90th day prior to such special meeting and (y) the tenth day following the day on which notice of the date of such special meeting was given or public disclosure of the date of such special meeting was made, whichever first occurs.

Annual Incentive Bonus *No Action By Written Consent*. Following Our certificate of incorporation provides that our stockholders may not act by written consent and may only act at duly called meetings of stockholders.

Undesignated Preferred Stock. As discussed above, our board of directors has the end ability to issue preferred stock with voting or other rights or preferences that could impede the success of each fiscal year any attempt to change control of our company. These and other provisions may have the effect of deferring hostile takeovers or delaying changes in control or management of us.

Delaware Business Combination Statute. We are subject to Section 203 of the Delaware General Corporation Law (the "DGCL") which prohibits a Delaware corporation from engaging in business combinations with an interested stockholder. An interested stockholder is generally defined as an entity or person beneficially owning 15% or more of the outstanding voting stock of the corporation or any entity or person affiliated with or controlling or controlled by such entity or person ("interested stockholder"). Section 203 provides that an interested stockholder may not engage in business combinations with the corporation for a period of three years after the date that such stockholder became an interested stockholder, with the following exceptions:

- before such date, the board of directors of the corporation approved either the business combination or the transaction that 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 at the time the transaction began, excluding for purposes of determining the voting stock outstanding (but not the outstanding voting stock owned by the interested stockholder) those shares owned (i) by persons who are directors and also officers and (ii) employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the approval plan will be tendered in a tender or exchange offer; or
- on or after such date, the business combination is approved by the Company's Board board of Directors in its sole discretion, you will be eligible directors and authorized at an annual or special meeting of the stockholders, and not by written consent, by the affirmative vote of at least 66 2/3% of the outstanding voting stock that is not owned by the interested stockholder.

In general, Section 203 defines business combinations to earn an incentive bonus, based on your performance include the following:

- any merger or consolidation involving the corporation and the Company's performance, each during interested stockholder;
- any sale, lease, transfer, pledge or other disposition of 10% or more of the applicable fiscal year, and assets of the corporation to or with the interested stockholder;
- subject to your continued employment certain exceptions, any transaction that results in good standing 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 or any class or series of the corporation beneficially owned by the interested stockholder; or
- the receipt by the interested stockholder of the benefit of any loss, advances, guarantees, pledges or other financial benefits by or through the corporation.

Exclusive Forum Selection. Our certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware (or, if the Court of Chancery of the State of Delaware does not have jurisdiction, the federal district court for the District of Delaware) shall, to the fullest extent permitted by law, be the sole and exclusive forum for (1) any derivative action or proceeding brought on behalf of our company, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers, other employees or stockholders to our company or our stockholders, (3) any action asserting a claim arising pursuant to any provision of the DGCL or as to which the DGCL confers jurisdiction on the date Court of payment Chancery of such incentive bonus. Your target annual incentive bonus opportunity shall be up to 40% the State of your base salary. Because of your start date, in accordance with the Company's policy, the first year you will be eligible for Delaware or (4) any action asserting a bonus is 2023.

Benefits. You may participate in the benefit programs that the Company establishes and makes available to its employees from time to time, subject to the terms and conditions of those programs. The Company's benefits programs are subject to change at any time in the Company's sole discretion. One of these benefit programs includes the Change in Control Policy adopted by the Board of Directors for Corporate Officers.

Vacation. You will be eligible for annual paid vacation of 20 days. Your accrual and use of vacation time will be claim arising pursuant and subject to any vacation provision of our certificate of incorporation or time off policy the Company may establish or modify from time to time. The Company's vacation policy is subject to change at any time in the Company's sole discretion.

Sick Time and Holiday Pay: As an eligible, full-time employee, you will also accrue 1.54 hours per pay period, or five (5) days per year, of sick days. In addition, the Company honors at least 11 holidays per year.

Equity Grants. Upon your Start Date, the Company shall grant to you a stock option (the "Option") under the Company's 2019 Equity Incentive Plan, bylaws (in each case, as it they may be amended from time to time (the "Plan"), to purchase 300,000 shares (subject to any adjustments for any stock splits, stock dividends, reverse stock splits time) or recapitalizations that are effected at any time during the period commencing after the date of this letter and ending on the grant date of the Option, the "Option Shares") of the Company's common stock, $0.001 par value per share (the "Common Stock"), at an exercise price equal to fair market value of the Common Stock, as determined by the Board of Directors of the Company, on the date of the grant of the Option (the "Grant Date").

Promptly after the Grant Date, the Company and you shall execute and deliver to each other the Company's then standard form of stock option agreement, evidencing the Option and the terms thereof.The Option shall be subject to, and governed by the terms, provisions, and restrictions on transfer internal affairs doctrine. Our certificate of incorporation further provides that, unless we consent in writing to the selection of an alternative forum, the federal district courts of the Plan, your stock option agreement, United States of America shall, to the fullest extent permitted by law, be the sole and exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act of 1933, as amended (the "Securities Act"). Neither of these choice of forum provisions would affect suits brought to enforce any liability or duty created by the Exchange Act or the rules and regulations thereunder, jurisdiction over which is exclusively vested by statute in the United States federal courts, or any other agreement to claim for which you shall become, or United States federal courts have exclusive jurisdiction. Although our certificate of incorporation contains the choice of forum provisions described above, it is possible that a court could rule that such provisions are required to become, a party pursuant to the terms of the Plan.

You may be awarded additional equity grants from time to time in accordance with normal business practice and in the sole discretion of the Company's CEO or Board of Directors. The terms of any future equity grant will be consistent with any plan under which they are granted and the terms of the applicable agreement under which the award(s) are granted.

Invention, Non-Disclosure, Non-Competition and Non-Solicitation Obligations. At or prior to the Start Date, you shall execute and deliver for the benefit of the Company the Invention and Non-Disclosure Agreement and, Non-Competition and Non-Solicitation Agreement in the forms attached to this letter.

At-Will Employment. This letter shall not be construed as an agreement, either express or implied, to employ you for any stated term, and shall in no way alter the Company's policy of employment at-will. Similarly, nothing in this letter shall be construed as an agreement, either express or implied, to pay you any compensation or grant you any benefit beyond the end of your employment with the Company, except as otherwise explicitly set

forth in this letter. This letter supersedes all prior understandings, whether written or oral, with respect to the subject matter of this letter.

Cooperation. During your employment with the Company and thereafter, you shall cooperate with the Company and be reasonably available to the Company with respect to continuing and/or future matters relating to your employment period with the Company and/or its affiliates, whether such matters are business-related, legal, regulatory or otherwise (including, without limitation, your appearing at the Company's request to give testimony without requiring service of a subpoena or other legal process, volunteering to the Company all pertinent information and turning over to the Company all relevant documents which are or may come into your possession). Following your employment term with the Company, the Company shall reimburse you for all reasonable out of pocket travel expenses incurred by you in rendering such services that are approved by the Company.

Representations. You hereby represent and warrant to the Company that the execution, delivery and performance of this offer letter by you does not and shall not conflict with, breach, violate or cause a default under any contract, agreement, instrument, order, judgment or decree to which you are a party or by which you are bound.

Entire Agreement. This letter constitutes the entire agreement and understanding between you and the Company with respect to the subject matter hereof and terminates and supersedes any and all prior agreements, understandings and representations, whether written or oral, by or between you and the Company which may have related to the subject matter hereof in any way, any of which are hereby terminated and cancelled and of no further force or effect without the payment of any consideration by or to either you or the Company.

Amendment. The provisions of this letter may be amended or waived only with the prior written consent of the Company and you, and no course of conduct or course of dealing or failure or delay by you or the Company in enforcing or exercising any of the provisions of this letter shall affect the validity, binding effect or enforceability of the letter or be deemed to be an implied waiver of any similar or dissimilar requirement, provision or condition of this letter at the same or any prior or subsequent time.

David, we look forward to having you join the Trevi leadership team. We have lots of exciting development work ahead of us, which hopefully ends in an FDA filing. Please indicate your acceptance of this letter of employment by signing a copy of this offer letter and returning it to us by Thursday November 10, 2022. I'm happy to discuss any of the terms of our offer.

Sincerely,

/s/ Jennifer L. Good

Jennifer L. Good

President & CEO

The foregoing correctly sets forth the terms of my at-will employment with Trevi. I am not relying on any representations other than those set forth above.

/s/David Clark 11/5/2022

NAME Date

Exhibit 10.16

Second Amendment to Lease

THIS SECOND AMENDMENT TO LEASE ("Second Amendment") dated November 21, 2022, ("Effective Date") by and between 195 Church Street Associates, LLC, a Connecticut limited liability corporation ("Landlord") and Trevi Therapeutics, Inc. ("Tenant").

WITNESSETH:

WHEREAS, Landlord entered into a certain Indenture of Lease with Tenant dated February 6th, 2013 (the "Original Lease") and with respect to certain office space located on the 14th floor of the Building comprised of 3,387 rentable square feet (the "Original Premises").

WHEREAS, Landlord entered into a certain First Amendment to Lease with Tenant dated December 5th, 2017 (the "First Amendment") and with respect to adding the Expansion Space to the Original Premises inapplicable for a total Demised Premises of 5,563 rentable square feet (the "14th Floor Premises") and extending the Term to February 28, 2023 (the "Current Termination Date"). particular claim or action.

WHEREAS, Landlord and Tenant wish to amend the Lease with regard to the size and location of the Demised Premises, the Term of the Lease, the fit up amount, the Fixed Rent, and the percentage of total rentable space.

NOW THEREFORE, in consideration of the terms and conditions of the Lease and the mutual covenants contained therein and herein, each of the parties hereto agrees as follows:

1. All capitalized terms not otherwise defined herein shall have the meaning ascribed to them in the Original Lease. The Original Lease, as amended by the First Amendment and this Second Amendment, is hereinafter referred to as the "Lease".

2. The Term is hereby extended for a period of five (5) years from the Current Termination Date, unless sooner terminated or otherwise extended in accordance with the terms of the Lease, to February 28, 2028 (the "Extended Term"). Tenant's obligation to pay Fixed Rent for the Expansion Space (as hereinafter defined) shall commence on the later to occur of (i) completion of all of the Expansion Conditions (as hereinafter defined) or (ii) March 1, 2023 (the "Expansion Space Commencement Date"). Except as otherwise provided in this

Second Amendment, the terms and conditions of the Extended Term shall be the same terms and conditions as are set forth in (and are last applicable under) the Original Lease.

As of the Expansion Space Commencement Date and continuing for the remainder of the Extended Term, the "Demised Premises", as such term is used in the Original Lease, shall include the entirety of the 16th floor of the Building, which Landlord represents is 12,500 rentable square feet measured pursuant to ANSI/BOMA Z65.1-2017 ("BOMA") and as shown on Exhibit A attached hereto (the "Expansion Space") (collectively, the "Demised Premises"). Landlord shall deliver to Tenant exclusive possession of the Expansion Space on the Expansion Space Commencement Date in the condition required hereunder. If any portion of the Expansion Space is ready for occupancy prior to the Expansion Space Commencement Date, Tenant will be permitted access to same without being obligated to

---

pay Fixed Rent or any additional rent therefor (except for electric costs as herein limited) until the Expansion Space Commencement Date, but subject to all other terms and covenants of the Lease. Landlord hereby warrants and represents that, as of the Expansion Space Commencement Date (or on such earlier date that Landlord delivers exclusive occupancy of the Expansion Space to Tenant), all of which shall be the "Expansion Conditions": (a) the Expansion Space shall be vacant, broom-clean and ready for Tenant's exclusive occupancy; (b) Landlord's Work (as herein defined) shall be substantially completed such that a final and unconditional certificate of completion permitting lawful occupancy has been duly issued, and such that Tenant may reasonably commence its business operations, subject only to punch list items that do not interfere with Tenant's business and shall be completed within thirty (30) days of the date of substantial completion; (c) all mechanical, electrical, plumbing, HVAC and life safety equipment and utility systems serving the Expansion Space shall be in good working order; (d) the Demised Premises shall be structurally sound and "water-tight"; (e) Tenant's access to the Demised Premises shall be reasonably secure and unimpeded; and (f) the Demised Premises shall be in compliance with all applicable laws, codes, statutes, ordinances, guidelines, rules, and regulations. Landlord's warranties and representations under this Paragraph shall survive the commencement of the Extended Term.

After the Expansion Space Commencement Date, Article 37 shall not be applicable to the 14th Floor Premises and Tenant shall reasonably promptly relocate its personal property to the Demised Premises. If Tenant fails to vacate the 14th Floor Premises within fifteen (15) business days of the Expansion Space Commencement Date, Tenant shall be obligated to continue to pay Rent for such space until it is vacated at the same rate as is required for the 14th Floor Premises in the Lease for the monthly period immediately preceding the Expansion Space

Commencement Date. The Renewal Options shall be available at the end of the Extended Term pursuant to compliance with Section 29.01, as amended by this Second Amendment.

3. Section 1.04 of the Lease shall be deleted in its entirety and the following shall be inserted in lieu thereof:

> "Tenant shall have the option to terminate this Lease provided that Tenant shall not at the time of the exercise of the hereinafter described option, be in default of any of the terms, covenants or conditions to be kept and performed on the part of Tenant under this Lease beyond applicable notice and cure periods. Such termination shall be effective on the last day of the thirty sixth (36th) month of the Extended Term (the "Termination Date"). To exercise this option to terminate, Tenant shall provide written notice to Landlord no later than the first day of the thirty-first (31st) month of the Extended Term and such notice shall be accompanied by a sum equal to three (3) months Fixed Rent at the then current rate, which is $90,249.99 and the unamortized Tenant Improvement Allowance of $670,000.00, unamortized brokerage fees (which at the time of signing of this amendment have not been calculated),and all free rent totaling $111,035.00. On or before the Termination Date, Tenant shall surrender possession of the Demised Premises to Landlord; time is of the essence in all respects of Tenant's obligations under this Section 1.04."

---

4. Landlord shall substantially complete all of the initial alterations and related improvements to the Demised Premises as mutually agreed upon by Landlord and Tenant and necessary for the conduct of Tenant's business therein (the "Landlord's Work").

5. Landlord, at its sole cost and expense, but subject to the Fit-Up Allowance,shall perform Landlord's Work so that it is substantially completed on or before the Expansion Space Commencement Date. Landlord's Work shall be performed by Landlord in a first-class manner as to workmanship, installation and materials. Landlord shall provide Tenant with a fit-up allowance of up to $670,000.00 ("Fit-Up Allowance"), which Fit-Up Allowance shall be used for the hard and soft costs of the Landlord's Work. Tenant shall, at its sole cost and expense, reimburse Landlord for any costs and expenses associated with Landlord's Work that exceeds the Fit-Up Allowance. Landlord has stated the Fit-Up Allowance will cover all costs associated with the plans and specifications for Landlord's Work based on the specifications and finishes within the building, including all fit and finishes and as more particularly described on Exhibit B attached hereto.

Landlord shall, on or before the thirtieth (30th) day following the Effective Date, submit to Tenant for Tenant's written approval final and complete dimensioned and detailed plans and specifications of partition layouts (including openings), colors, and per

Tenant's furniture plan, including any and all budget information as may be reasonably necessary to determine the budget in connection with Landlord's Work (such plans and specifications are collectively referred to herein as the "Plans"). Landlord shall submit the Plans to Tenant in form, quality and quantity acceptable for the purposes of filing for a building permit with the Building Department of the City of New Haven, and such plans shall be signed and sealed by an architect licensed in the State of Connecticut. After receipt of the Plans, Tenant shall either approve in writing the Plans or designate by notice to Landlord the specific design or cost changes required to be made to the Plans which would result in its approval of the Plans. Landlord shall cause its architect to make the changes required by Tenant and deliver revised Plans to Tenant for approval within five (5) business days of receipt of Tenant's notice. This procedure shall be repeated until the Plans are approved in writing by Tenant. The existing mechanicals, electrical circuitry plans, ceiling and lighting shall remain and be modified by Landlord as part of the Landlord's Work.

6. Fixed Rent for the Extended Term shall be payable in accordance with the schedule below and the applicable terms of the Lease:

Months	Per Square Foot	Annual Rent	Monthly Rent
1-12	$27.50	$275,000 Based on a 10,000 square foot Premises (i.e., free rent of $68,750)	$22,916.67
13-24	$28.19	$310,090	$25,840.83

Based on a 11,000 square foot Premises (i.e., free rent of $42,285)			

25-36	$28.89	$361,125	$30,093.75
37-48	$29.61	$370,125	$30,843.75
49-60	$30.35	$379,375	$31,614.58

Notwithstanding anything to the contrary in the Lease, in all years of the Extended Term all rents are quoted exclusive of pro rata share of electric costs. Tenant shall be responsible for additional rent for its proportionate share of all electric costs, said share not to exceed $31,250.00 per year.

7. Effective as of the Expansion Premises Commencement Date, Section 2.03(b) of the Lease shall be deleted in its entirety and replaced with the following:

"Subject to the provisions herein, effective as of the Expansion Space Commencement Date, Tenant shall pay the amount equal to 5.1% (the percentage of total rentable space in the Building leased by Tenant hereunder) of the amount by which Building Operating and real-estate taxes paid or incurred by Landlord during any calendar year during the Extended Term hereof exceed Operating Expenses for the base year. Landlord represents that the total rentable area of the Building measures 245,000 rentable square feet per BOMA. The "base year" shall be the calendar year ending December 31, 2023. Notwithstanding anything to the contrary in the foregoing, Tenant's pro rata share of electric costs shall not exceed $31,250.00 for each year of the Extended Term and the Additional Renewal Term."

8. Effective as of the Expansion Premises Commencement Date, Section 2.04(A)(9) of the Lease shall be deleted in its entirety and replaced with the following:

"Costs (including applicable taxes) for electricity and other utilities provided that Tenant's pro rata share of electric costs shall not exceed $31,250.00 for any year of the Extended Term."

9. Effective as of the Expansion Premises Commencement Date, Section 5.01 of the Lease shall be deleted in its entirety and the following shall be inserted in lieu thereof:

"Landlord shall make its best efforts to provide 25 parking spaces for Tenant's use in the Connecticut Financial Center parking garage located adjacent and below the Building at current market rates per space and at Tenant's sole cost. Including in such parking allocation, Landlord shall provide four (4) spaces located on level P2 of said garage. Tenant shall pay for said spaces, at its sole cost and expense, directly to the garage operator.

.

10. The parties hereto agree that Evan O'Brien of Cushman & Wakefield represents the

Landlord and Robert H. Motley of Cushman & Wakefield represents the Tenant's interest in negotiations of the Second Amendment and shall be paid by Landlord pursuant to a separate agreement. The parties hereby acknowledge that these brokers/agents are the only parties with any claim to a commission arising out of this transaction and shall indemnify the other for any adverse claims to the contrary.

11. Effective as of the date hereof, the first and second paragraphs of Section 29.01 of the Lease are hereby deleted in its entirety and replaced with the following:

> "Effective as of the Expansion Space Commencement Date, if, immediately prior to the expiration of the Extended Term provided in Article 1, this Lease (for purposes of this Article 29 only, the "Term" is hereinafter called the "Extended Term") shall be in full force and effect and provided Tenant not less than nine (9) months prior to the expiration of the Extended Term shall have given Landlord written notice of Tenant's interest in renewing this Lease, and upon receipt of such valid notice, the lease term shall be extended for a further term of five (5) years (hereinafter called the "Additional Renewal Term") commencing upon the expiration of the Extended Term and ending on the day preceding the fifth (5th) anniversary of the commencing of the Additional Renewal Term, consistent with the terms of this Lease, as amended, other than Fixed Rent which shall be at the Fair Rental Value as described in the remainder of this Section 29.01 and the base year which shall be the first calendar year of the Additional Renewal Term. "

12. Section 29.02 is hereby deleted in its entirety.

13. Except as modified herein, all terms, covenants, agreements and conditions of the Lease shall remain unchanged. The rights, privileges, duties and obligations of the parties under the Lease shall, except as modified above, remain unchanged and in full force and effect and nothing herein contained shall operate to release Tenant from its obligations under the Lease.

14. This Second Amendment is an integrated document and all terms and provisions as to the subject matter hereof are embodied herein and shall not be varied.

15. This Second Amendment may be signed or electronically executed in any number of counterparts. Each executed counterpart shall be deemed an original hereof and all such executed counterparts shall together constitute but one and the same instrument, which instrument shall for all purposes be sufficiently evidenced by any such executed counterpart.

16. This Second Amendment shall be binding upon and inure to the benefit of the parties hereto and their respective successors and assigns, provided that nothing contained herein shall permit any transfer, assignment or sublease, contrary to the provisions of the Lease.

17. This Second Amendment is made, executed and delivered in the State of Connecticut and it is the specific desire and intention of the parties that it shall in all respects be construed under the laws of the State of Connecticut.

IN WITNESS WHEREOF, the parties hereto have set their hands and seals as of the day and year first above written

LANDLORD: TENANT:

195 CHURCH STREET ASSOCIATES, LLC TREVI THERAPEUTICS, INC.

BY: /s/ Paul Denz_____ BY: /s/ Lisa Delfini_____

Name: Paul Denz Name: Lisa Delfini

ITS: Manager ITS: Authorized Signatory

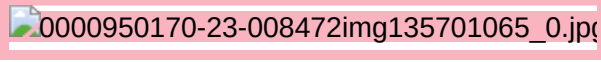
Date: 11/21/2022 Date: 11/21/2022

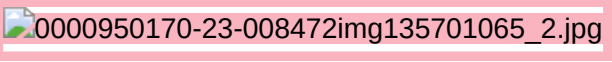
EXHIBIT A

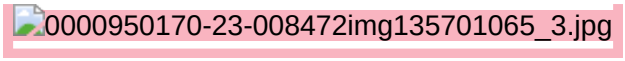
FLOOR PLAN

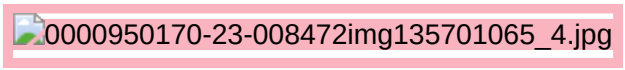
EXHIBIT B

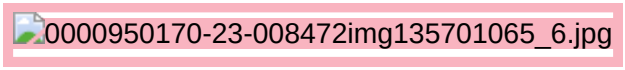
PLANS & SPECIFICATIONS











4895-9289-7840, v. 9

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the following Registration Statements:

(1) Registration Statement Statements (Form S-1 No. 333-257747) S-3 Nos. 333-260279, 333-260820, 333-264614 and 333-273030) of Trevi Therapeutics, Inc.,

(2) Registration Statements (Form S-3 Nos. 333-239499, 333-260279, 333-260820 and 333-264614) of Trevi Therapeutics, Inc.,

(3) Registration Statement (Form S-8 No. 333-231260) pertaining to the 2012 Stock Incentive Plan, as amended, the 2019 Stock Incentive Plan and the 2019 Employee Stock Purchase Plan of Trevi Therapeutics, Inc., and

(4) (3) Registration Statements (Form S-8 Nos. 333-237193, 333-257729, 333-264615 and 333-264615) 333-271839) pertaining to the 2019 Stock Incentive Plan and the 2019 Employee Stock Purchase Plan of Trevi Therapeutics, Inc.;

of our report dated March 16, 2023 March 20, 2024, with respect to the consolidated financial statements of Trevi Therapeutics, Inc. included in this Annual Report (Form 10-K) of Trevi Therapeutics, Inc. for the year ended December 31, 2022 December 31, 2023.

/s/ Ernst & Young LLP
Hartford, Connecticut
March 16, 2023 20, 2024

Exhibit 31.1

CERTIFICATION PURSUANT TO RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934, AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Jennifer L. Good, certify that:

1. I have reviewed this Annual Report on Form 10-K of Trevi 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: March 16, 2023 March 20, 2024

By: /s/ Jennifer L. Good

Jennifer L. Good

President and Chief Executive Officer

(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION PURSUANT TO RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934, AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Lisa Delfini, certify that:

1. I have reviewed this Annual Report on Form 10-K of Trevi 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: March 16, 2023 March 20, 2024

By: /s/ Lisa Delfini

Lisa Delfini

Chief Financial Officer

(Principal Financial 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 on Form 10-K of Trevi Therapeutics, Inc. (the "Company") for the period ended December 31, 2022 December 31, 2023, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Jennifer L. Good, President and Chief Executive Officer 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 her 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 and results of operations of the Company.

Date: March 16, 2023 March 20, 2024

By: /s/ Jennifer L. Good

Jennifer L. Good

President and Chief Executive Officer

(Principal Executive Officer)

Exhibit 32.2

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 on Form 10-K of Trevi Therapeutics, Inc. (the "Company") for the period ended December 31, 2022 December 31, 2023, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Lisa Delfini, Chief Financial Officer 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 her 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 and results of operations of the Company.

Date: March 16, 2023 March 20, 2024

By: /s/ Lisa Delfini
Lisa Delfini
Chief Financial Officer
(Principal Financial Officer)

Exhibit 97

TREVI THERAPEUTICS, INC.

Dodd-Frank Compensation Recovery Policy

This Compensation Recovery Policy (this "Policy") is adopted by Trevi Therapeutics, Inc. (the "Company") in accordance with Nasdaq Listing Rule 5608 ("Rule 5608"), which implements Rule 10D-1 under the Securities Exchange Act of 1934, as amended (the "Exchange Act") (as promulgated pursuant to Section 954 of the Dodd-Frank Wall Street Reform and Consumer Protection Act of 2010).

1. Definitions

(a)**"Accounting Restatement"** means a requirement that the Company prepare an accounting restatement due to the material noncompliance of the Company with any financial reporting requirement under the U.S. federal securities laws, including any required accounting restatement to correct an error in previously issued financial statements 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. Changes to the Company's financial statements that do not represent error corrections are not an Accounting Restatement, including: (A) retrospective application of a change in accounting principle; (B) retrospective revision to reportable segment information due to a change in the structure of the Company's internal organization; (C) retrospective reclassification due to a discontinued operation; (D) retrospective application of a change in reporting entity, such as from a reorganization of entities under common control; and (E) retrospective revision for stock splits, reverse stock splits, stock dividends or other changes in capital structure.

(b)**"Committee"** means the Compensation Committee of the Company's Board of Directors (the "Board").

(c)**"Covered Person"** means a person who served as an Executive Officer at any time during the performance period for the applicable Incentive-Based Compensation.

(d)**"Erroneously Awarded Compensation"** means the amount of Incentive-Based Compensation that was Received that exceeds the amount of Incentive-Based Compensation that otherwise would have been Received had the amount of Incentive-Based Compensation been determined based on the restated amounts, computed without regard to any taxes paid by the Covered Person or by the Company on the Covered Person's behalf. 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 amount of Erroneously Awarded Compensation will be based on a reasonable estimate by the Committee of the effect of the Accounting Restatement on the stock price or total shareholder return upon which the Incentive-Based Compensation was Received. The Company will maintain documentation of the determination of that reasonable estimate and provide such documentation to Nasdaq.

1

(e)**“Executive Officer”** meansthe Company’s officers as defined in Rule 16a-1(f) under the Exchange Act

(f)**“Financial Reporting Measures”** means (A) measures that are determined and presented in accordance with the accounting principles used in preparing the Company’s financial statements, and any measures that are derived wholly or in part from such measures (whether or not such measures are presented within the Company’s financial statements or included in a filing made with the U.S. Securities and Exchange Commission), (B) stock price and (C) total shareholder return.

(g)**“Incentive-Based Compensation”** means any compensation that is granted, earned, or vested based wholly or in part upon the attainment of a Financial Reporting Measure. Incentive-Based Compensation does not include base salary, bonus awards that are discretionary or based on subjective goals or goals unrelated to Financial Reporting Measures, equity awards that vest exclusively upon completion of a specified employment period, without any performance condition, and equity awards that vest based on milestones or performance conditions that are unrelated to Financial Reporting Measures.

(h)Incentive-Based Compensation is deemed to be **“Received”** in the Company’s fiscal period during which the Financial Reporting Measure specified in the applicable Incentive-Based Compensation award is attained, even if the payment or grant of the Incentive-Based Compensation occurs after the end of that period or is subject to additional time-based vesting requirements.

(i) **“Recovery Period”** means the three completed fiscal years immediately preceding the earlier of: (A) the date the Board, a committee of the Board, or the officer or officers of the Company authorized to take such action if Board action is not required, concludes, or reasonably should have concluded, that the Company is required to prepare an Accounting Restatement; or (B) the date a court, regulator, or other legally authorized body directs the Company to prepare an Accounting Restatement. In addition, if there is a change in the Company’s fiscal year end, the Recovery Period will also include any transition period to the extent required by Rule 5608.

2. Recovery of Erroneously Awarded Compensation

Subject to the terms of this Policy and the requirements of Rule 5608, if the Company is required to prepare an Accounting Restatement, the Company will attempt to recover, reasonably promptly from each Covered Person, any Erroneously Awarded Compensation that was Received by such Covered Person during the Recovery Period pursuant to Incentive-Based Compensation that is subject to this Policy.

3. Interpretation and Administration

(a)Role of the Committee. This Policy will be interpreted by the Committee in a manner that is consistent with Rule 5608 and any other applicable law and will otherwise be interpreted in the business judgment of the Committee. All decisions and interpretations of the Committee that are consistent with Rule 5608 will be final and binding.

(b)Compensation Not Subject to this Policy. This Policy does not apply to Incentive-Based Compensation that was Received before October 2, 2023.

(c)Determination of Means of Recovery. Subject to the requirement that recovery be made reasonably promptly, the Committee will determine the appropriate means of recovery, which may vary between Covered Persons or based on the nature of the applicable Incentive-Based Compensation, and which may involve, without limitation, establishing a deferred repayment plan or setting off against current or future compensation otherwise payable to the Covered Person. Recovery of Erroneously Awarded Compensation will be made without regard to income taxes paid by the Covered Person or by the Company on the Covered Person’s behalf in connection with such Erroneously Awarded Compensation.

(d)No Indemnification or Company-Paid Insurance. The Company will not indemnify any Covered Person against the loss of Erroneously Awarded Compensation and will not pay or reimburse any Covered Person for the purchase of a third-party insurance policy to fund potential recovery obligations.

(e)Interaction with Other Clawback Provisions. The Company will be deemed to have recovered Erroneously Awarded Compensation in accordance with this Policy to the extent the Company actually

receives such amounts pursuant to any other Company policy, program or agreement, pursuant to Section 304 of the Sarbanes-Oxley Act or otherwise.

(f) No Limitation on Other Remedies. Nothing in this Policy will be deemed to limit the Company's right to terminate employment of any Covered Person, to seek recovery of other compensation paid to a Covered Person, or to pursue other rights or remedies available to the Company under applicable law.

Adopted by the Board on [date].

DISCLAIMER

THE INFORMATION CONTAINED IN THE REFINITIV CORPORATE DISCLOSURES DELTA REPORT™ IS A COMPARISON OF TWO FINANCIALS PERIODIC REPORTS. THERE MAY BE MATERIAL ERRORS, OMISSIONS, OR INACCURACIES IN THE REPORT INCLUDING THE TEXT AND THE COMPARISON DATA AND TABLES. IN NO WAY DOES REFINITIV OR THE APPLICABLE COMPANY ASSUME ANY RESPONSIBILITY FOR ANY INVESTMENT OR OTHER DECISIONS MADE BASED UPON THE INFORMATION PROVIDED IN THIS REPORT. USERS ARE ADVISED TO REVIEW THE APPLICABLE COMPANY'S ACTUAL SEC FILINGS BEFORE MAKING ANY INVESTMENT OR OTHER DECISIONS.

REFINITIV