# UNITED STATES
# SECURITIES AND EXCHANGE COMMISSION
**WASHINGTON, DC 20549**

# FORM 10-Q

**(Mark One)**

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

**For the quarterly period ended September 30, 2021**

**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, 14th Floor New Haven, Connecticut** | **06510** |
| **(Address of principal executive offices)** | **(Zip Code)** |

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

**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** |

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 is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

As of November 10, 2021, the registrant had 25,846,577 shares of common stock, $0.001 par value per share, outstanding.

## CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS AND INDUSTRY DATA

This Quarterly Report on Form 10-Q contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical fact, contained in this Quarterly Report on Form 10-Q, 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,” “estimate,” “expect,” “intend,” “may,” “might,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “would,” “could,” “continue” 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 Quarterly Report on Form 10-Q include, among other things, statements about:

- our ongoing clinical trials, including our Phase 2b/3 PRISM trial of Haduvio (nalbuphine ER) for the treatment of pruritus associated with prurigo nodularis and our Phase 2 CANAL trial for the treatment of chronic cough in patients with idiopathic pulmonary fibrosis;
- our plans to develop and, if approved, subsequently commercialize Haduvio for the treatment of pruritus associated with prurigo nodularis or for other serious neurologically mediated conditions;
- 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 and capital expenditure requirements with our cash and cash equivalents and to continue as a going concern;
- 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;
- our ability to establish and maintain collaborations or obtain additional funding; and
- the impact of the pandemic caused by the novel coronavirus, or COVID-19, which pandemic we refer to as the COVID-19 pandemic, on our clinical trials, business and operations and our response to the COVID-19 pandemic.

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

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 Quarterly Report on Form 10-Q are the property of their respective owners. Solely for convenience, some of the trademarks, service marks and trade names referred to in this Quarterly Report on Form 10-Q 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 nalbuphine ER investigational product and therefore plan to use that name when we refer to nalbuphine ER going forward.

## 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 Quarterly Report on Form 10-Q and should be carefully considered, together with other information in this Quarterly Report on Form 10-Q 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 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.

- We have incurred significant losses since inception and expect to continue to incur significant and increasing losses for 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 have identified conditions and events that raise substantial doubt about our ability to continue as a going concern.

- Our existing indebtedness, together with our other financial obligations and contractual commitments, could adversely affect our financial condition and restrict our future operations. For instance, if we fail to receive positive data in our Phase 2b/3 PRISM trial or fail to meet certain minimum cash or equity raise requirements under our loan facility with Silicon Valley Bank, or SVB, which loan facility we refer to as the SVB Term Loan, we will be required to deposit unrestricted and unencumbered cash equal to 100% of the principal amount of the indebtedness then outstanding in a cash collateral account controlled by SVB, which can be used by SVB to prepay the SVB Term Loan at any time and would reduce the amounts available to fund working capital, capital expenditures, product development efforts and general corporate purposes.

- 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. In addition, the development of Haduvio for the treatment of pruritus associated with prurigo nodularis is currently significantly more advanced than our other target indications. If we are not successful in developing and commercializing Haduvio for the treatment of pruritus associated with prurigo nodularis, our business could also be substantially harmed.

- We have experienced delays and difficulties in the enrollment of subjects in our clinical trials, including our Phase 2b/3 PRISM trial and our Phase 2 CANAL trial. If we experience further delays or difficulties in the enrollment of subjects in clinical trials, our receipt of necessary regulatory approvals could be 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 with prurigo nodularis and subjects are generally only able to enroll in a single trial at a time. In addition, many patients use various treatments off-label to treat pruritus associated with 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.

- Our approach to the development and commercialization of Haduvio to treat serious neurologically mediated conditions is unproven.

- 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.

- Our Phase 2 clinical trial of Haduvio for the treatment of pruritus associated with prurigo nodularis may not be predictive of the results of our Phase 2b/3 PRISM trial, including due to the small subject size of the Phase 2 clinical trial, the discontinuation rate among subjects in the Phase 2 clinical trial, the limited number of subjects who completed treatment in

the Phase 2 clinical trial and differences in the design of the Phase 2 clinical trial and the PRISM trial, including the longer treatment period for Haduvio being used in the PRISM trial.

- Adverse events or undesirable side effects caused by, or other unexpected properties of, Haduvio or any future project 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 be susceptible to side effects associated with drugs having either of those mechanisms of action, including psychiatric side 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 a warning for serious, life-threatening or fatal respiratory depression and Haduvio, if approved for marketing in any indication, will likely carry a similar label.

- 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 plan to conduct a human abuse liability, or HAL, study to further characterize the abuse potential of oral nalbuphine. If the results of the HAL 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 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 Haduvio 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 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 face substantial competition, which may result in others developing or commercializing products before or more successfully than we do.

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

- We contract with third parties for the manufacture, storage, packaging and distribution 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 and any future product candidates.

- If we fail to comply with our obligations under our existing and any future intellectual property licenses with third parties, including our licenses with Endo Pharmaceuticals Inc. and with Rutgers, the State University of New Jersey, 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 the 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 products similar or identical to such product candidate and our ability to successfully commercialize such product candidate may 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.

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## PART I—FINANCIAL INFORMATION

**Item 1. Financial Statements.**

**Trevi Therapeutics, Inc.**
**Condensed Consolidated Balance Sheets**
**(unaudited)**
**(Amounts in thousands, except share and per share amounts)**

| | September 30, 2021 | December 31, 2020 |
|---|---|---|
| **Assets** | | |
| Current assets: | | |
| Cash and cash equivalents | $ 29,318 | $ 45,001 |
| Prepaid expenses and other current assets | 1,389 | 1,268 |
| Total current assets | 30,707 | 46,269 |
| Deferred offering costs | 419 | 284 |
| Operating lease right-of-use asset | 156 | 227 |
| Security deposits and other non-current assets | 248 | 248 |
| Property, equipment and leasehold improvements, net | 66 | 103 |
| Total assets | $ 31,596 | $ 47,131 |
| **Liabilities and stockholders' equity** | | |
| Current liabilities: | | |
| Accounts payable | $ 2,233 | $ 2,016 |
| Accrued expenses | 3,314 | 3,426 |
| Term loan - current portion | 4,083 | — |
| Term loan derivative liability - current portion | 167 | — |
| Operating lease liability - current portion | 116 | 113 |
| Total current liabilities | 9,913 | 5,555 |
| Term loan - long term portion | 10,245 | 13,954 |
| Term loan derivative liability - long term portion | — | 196 |
| Operating lease liability - long term portion | 58 | 144 |
| Total liabilities | 20,216 | 19,849 |
| Commitments and contingencies (Note 11) | | |
| Stockholders' equity: | | |
| Preferred stock: $0.001 par value; 5,000,000 shares authorized at September 30, 2021 and December 31, 2020; no shares issued or outstanding at September 30, 2021 or December 31, 2020. | — | — |
| Common stock: $0.001 par value; 200,000,000 shares authorized at September 30, 2021 and December 31, 2020; and 21,621,524 and 18,546,786 shares issued and outstanding at September 30, 2021 and December 31, 2020, respectively. | 22 | 19 |
| Additional paid-in capital | 183,755 | 174,240 |
| Accumulated deficit | (172,397) | (146,977) |
| Total stockholders' equity | 11,380 | 27,282 |
| Total liabilities and stockholders' equity | $ 31,596 | $ 47,131 |

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

**Trevi Therapeutics, Inc.**
**Condensed Consolidated Statements of Operations**
**(unaudited)**
**(Amounts in thousands, except share and per share amounts)**

| | Three Months Ended September 30, | | Nine Months Ended September 30, | |
|---|---|---|---|---|
| | 2021 | 2020 | 2021 | 2020 |
| Operating expenses: | | | | |
| Research and development | $ 4,718 | $ 4,828 | $ 16,805 | $ 15,768 |
| General and administrative | 2,229 | 2,416 | 7,398 | 7,528 |
| Total operating expenses | 6,947 | 7,244 | 24,203 | 23,296 |
| Loss from operations | (6,947) | (7,244) | (24,203) | (23,296) |
| Other (expense) income: | | | | |
| Change in fair value of term loan derivative liability | (5) | — | 29 | — |
| Other expense | — | — | (375) | — |
| Interest income | 2 | 3 | 7 | 174 |
| Interest expense | (303) | (148) | (893) | (148) |
| Total other (expense) income, net | (306) | (145) | (1,232) | 26 |
| Loss before income taxes | (7,253) | (7,389) | (25,435) | (23,270) |
| Income tax (expense) benefit | (2) | 11 | 15 | 35 |
| Net loss | $ (7,255) | $ (7,378) | $ (25,420) | $ (23,235) |
| Basic and diluted net loss per common share outstanding | $ (0.34) | $ (0.41) | $ (1.25) | $ (1.30) |
| Weighted average common shares used in net loss per share attributable to common stockholders, basic and diluted | 21,607,979 | 18,134,886 | 20,390,852 | 17,935,865 |

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

**Trevi Therapeutics, Inc.**
**Condensed Consolidated Statements of Stockholders' Equity**
**(unaudited)**
**(Amounts in thousands, except share amounts)**

| | Common Stock | | Additional Paid-in Capital | Accumulated Deficit | Total Stockholders' Equity |
|---|---|---|---|---|---|
| | Shares | Amount | | | |
| **Balance at June 30, 2021** | 21,459,498 | $ 21 | $ 182,857 | $ (165,142) | $ 17,736 |
| Stock-based compensation | — | — | 540 | — | 540 |
| Issuance of common stock under the at-the-market sales agreement, net of commissions and allocated fees | 162,026 | 1 | 358 | — | 359 |
| Net loss | — | — | — | (7,255) | (7,255) |
| **Balance at September 30, 2021** | 21,621,524 | $ 22 | $ 183,755 | $ (172,397) | $ 11,380 |
| | | | | | |
| **Balance at June 30, 2020** | 17,851,152 | $ 18 | $ 170,095 | $ (130,076) | $ 40,037 |
| Stock-based compensation | — | — | 588 | — | 588 |
| Issuance of common stock from exercise of stock options | 3,158 | — | 7 | — | 7 |
| Issuance of common stock under the at-the-market sales agreement, net of commissions and allocated fees | 466,758 | — | 2,364 | — | 2,364 |
| Net loss | — | — | — | (7,378) | (7,378) |
| **Balance at September 30, 2020** | 18,321,068 | $ 18 | $ 173,054 | $ (137,454) | $ 35,618 |

| | Common Stock | | Additional Paid-in Capital | 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 | — | — | 2,003 | — | 2,003 |
| Issuance of common stock under the at-the-market sales agreement, net of commissions and allocated fees | 2,895,518 | 3 | 7,120 | — | 7,123 |
| Issuance of common stock from Employee Stock Purchase Plan | 9,132 | — | 17 | — | 17 |
| Issuance of common stock to Lincoln Park Capital Fund (see Note 7) | 170,088 | — | 375 | — | 375 |
| Net loss | — | — | — | (25,420) | (25,420) |
| **Balance at September 30, 2021** | 21,621,524 | $ 22 | $ 183,755 | $ (172,397) | $ 11,380 |
| | | | | | |
| **Balance at December 31, 2019** | 17,834,570 | $ 18 | $ 168,746 | $ (114,219) | $ 54,545 |
| Stock-based compensation | — | — | 1,907 | — | 1,907 |
| Issuance of common stock from exercise of stock options | 18,343 | — | 34 | — | 34 |
| Issuance of common stock from Employee Stock Purchase Plan | 1,397 | — | 3 | — | 3 |
| Issuance of common stock under the at-the-market sales agreement, net of commissions and allocated fees | 466,758 | — | 2,364 | — | 2,364 |
| Net loss | — | — | — | (23,235) | (23,235) |
| **Balance at September 30, 2020** | 18,321,068 | $ 18 | $ 173,054 | $ (137,454) | 35,618 |

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

**Trevi Therapeutics, Inc.**
**Condensed Consolidated Statements of Cash Flows**
**(unaudited)**
**(Amounts in thousands)**

| | Nine Months Ended September 30, | |
|---|---|---|
| | **2021** | **2020** |
| **Operating activities:** | | |
| Net loss | $ (25,420) | $ (23,235) |
| Adjustments to reconcile net loss to net cash used in operating activities: | | |
| Depreciation | 38 | 34 |
| Change in fair value of term loan derivative liability | (29) | — |
| Accretion/accrual of term loan discounts and debt issuance costs | 442 | 68 |
| Other expense related to transaction with Lincoln Park Capital Fund, LLC | 375 | — |
| Stock-based compensation | 2,003 | 1,907 |
| Changes in operating assets and liabilities: | | |
| Prepaid expenses and other current assets | (122) | 323 |
| Accounts payable | 216 | (341) |
| Accrued expenses and other liabilities | (220) | 1,168 |
| Net cash used in operating activities | (22,717) | (20,076) |
| **Investing activities:** | | |
| Purchases of property, equipment and leasehold improvements | — | (27) |
| Net cash used in investing activities | — | (27) |
| **Financing activities:** | | |
| Proceeds from term loan | — | 14,000 |
| Payments of financing costs of term loan | (68) | (53) |
| Proceeds from at-the-market sales, net of commissions | 7,505 | 2,442 |
| Proceeds from exercises of stock options | — | 34 |
| Proceeds from employee stock purchase plan | 17 | 3 |
| Payments of offering costs | (420) | (343) |
| Net cash provided by financing activities | 7,034 | 16,083 |
| Net decrease in cash and cash equivalents | (15,683) | (4,020) |
| Cash and cash equivalents at beginning of period | 45,001 | 57,313 |
| Cash and cash equivalents at end of period | $ 29,318 | $ 53,293 |

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

## 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 (nalbuphine ER) to treat serious neurologically mediated conditions. The Company is currently developing Haduvio for the treatment of chronic pruritus associated with prurigo nodularis and chronic cough in patients with idiopathic pulmonary fibrosis ("IPF"). The Company is also developing Haduvio in levodopa-induced dyskinesia ("LID") in patients with Parkinson's disease. 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 itch, cough and certain movement disorders. 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 classified as a controlled substance in the U.S. and most of Europe.

***Liquidity***

In accordance with Accounting Standards Update ("ASU") No. 2014-15, *Disclosures of Uncertainties about an Entity's Ability to Continue as a Going Concern (Subtopic 205-40)* ("ASU No. 2014-15"), management must evaluate whether there are conditions or events, considered in the aggregate, that raise substantial doubt about the Company's ability to continue as a going concern within one year after the date that the financial statements are issued. This evaluation initially does not take into consideration the potential mitigating effect of management's plans that have not been fully implemented as of the date the financial statements are issued. When substantial doubt exists under this methodology, management evaluates whether the mitigating effect of its plans sufficiently alleviates substantial doubt about the Company's ability to continue as a going concern. The mitigating effect of management's plans, however, is only considered if both (1) it is probable that the plans will be effectively implemented within one year after the date that the financial statements are issued and (2) it is probable that the plans, when implemented, will mitigate the relevant conditions or events that raise substantial doubt about the entity's ability to continue as a going concern within one year after the date that the financial statements are issued. Generally, to be considered probable of being effectively implemented, the plans must have been approved before the date that the financial statements are issued.

The Company's Condensed Consolidated Financial Statements have been prepared on a going concern basis, which contemplates the continuity of operations, realization of assets and the satisfaction of liabilities and commitments in the ordinary course of business. Since inception, the Company has financed its operations primarily through private placements of 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 7) with SVB Leerink LLC that the Company entered into in June 2020 and the term loan facility with Silicon Valley Bank ("SVB") that the Company entered into in August 2020. The Company has incurred recurring losses since inception, including net losses of $25.4 million for the nine months ended September 30, 2021 and $32.8 million for the year ended December 31, 2020. As of September 30, 2021, the Company had cash and cash equivalents of $29.3 million compared to $45.0 million of cash and cash equivalents as of December 31, 2020. The Company has incurred losses and negative cash flows from operations and had an accumulated deficit of $172.4 million as of September 30, 2021. The Company expects to continue to incur losses for the foreseeable future.

As of November 10, 2021, the date of issuance of these Condensed Consolidated Financial Statements, the Company believes that its cash and cash equivalents as of September 30, 2021, together with the proceeds from the Company's October 2021 private placements (Note 12), will not be sufficient to fund its operating expenses and capital expenditure requirements for 12 months from the date of issuance of these Condensed Consolidated Financial Statements. The Company plans to seek to address this condition by raising additional capital to finance its operations. The future viability of the Company is dependent on its ability to raise additional capital to finance its operations. Although the Company has been successful in raising capital in the past, there is no assurance that it will be successful in obtaining such additional financing. Therefore, it is not considered probable, as defined in ASU No. 2014-15, that the Company's plans to raise additional capital will alleviate the substantial doubt regarding its ability to continue as a going concern.

To execute its business plans, the Company will need substantial funding to support its continuing operations and pursue its growth strategy. Until such time that the Company can generate significant revenue from product sales, if ever, the Company expects

to finance its operations through the sale of common stock in public offerings and/or private placements, debt financings or other capital sources, including collaborations with other companies or other strategic transactions. The Company may not be able to obtain financing when needed on acceptable terms or at all. The terms of any financing may adversely affect the holdings or the rights of the Company's stockholders. If the Company is unable to obtain funding, the Company could be forced to delay, reduce or abandon its product development programs or commercialization efforts, which could adversely affect its business prospects.

## 2. Summary of Significant Accounting Policies

### *Basis of Presentation*

The accompanying unaudited interim Condensed Consolidated Financial Statements for the three and nine months ended September 30, 2021 and 2020 included herein, have been prepared in accordance with accounting principles generally accepted in the U.S. ("GAAP") for interim financial information and the rules and regulations of the Securities and Exchange Commission ("SEC") for interim information. Certain prior year balances have been reclassified to conform to the current year presentation. Such reclassifications did not affect loss from operations or net loss. Certain information and footnote disclosures typically prepared in accordance with GAAP have been condensed or omitted pursuant to SEC rules and regulations. The accompanying unaudited Condensed Consolidated Financial Statements and notes should be read in conjunction with the audited consolidated financial statements and related notes included in the Company's Annual Report on Form 10-K for the year ended December 31, 2020 (the "Annual Report on Form 10-K").

The accompanying Condensed 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 September 30, 2021 for potential recognition or disclosure in the Condensed Consolidated Financial Statements. Refer to Note 12 for disclosure related to events occurring subsequent to September 30, 2021.

### *Use of Estimates*

The preparation of financial statements in conformity with 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 Condensed 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. 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. On an ongoing basis, management evaluates its estimates in light of changes in circumstances, facts and experience. Changes in estimates are recorded in the period in which they become known. Actual results could differ from those estimates. The inputs into the Company's estimates also considered the economic implications of the COVID-19 pandemic on the Company's estimates.

### *Unaudited Interim Financial Information*

The accompanying interim Condensed Consolidated Balance Sheet as of September 30, 2021 and the Condensed Consolidated Statements of Operations, the Condensed Consolidated Statements of Stockholders' Equity and the Condensed Consolidated Statements of Cash Flows for the three and nine months ended September 30, 2021 and 2020 are unaudited. The unaudited interim Condensed Consolidated Financial Statements have been prepared on the same basis as the audited annual consolidated financial statements and, in the Company's opinion, reflect all adjustments, which include only normal recurring adjustments, necessary for the fair statements of its financial position as of September 30, 2021 and the results of its operations and its cash flows for the three and nine months ended September 30, 2021 and 2020. The results for the three and nine months ended September 30, 2021 and 2020 are not necessarily indicative of results to be expected for the year ending December 31, 2021 or any other interim period or any future year or period.

### *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.

### *Fair Value Measurements*

The Company's financial instruments have consisted of cash and cash equivalents, other current assets, accounts payable, accrued expenses, term loans and term loan derivative liability (Note 6). 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. The carrying amount of the term loan approximates its fair value due to its floating market-based interest rate. The term loan derivative liability is recorded at fair value, which is estimated utilizing a probability-weighted cash flow approach (Note 6).

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.

The following table summarizes the financial assets and financial liabilities measured at fair value on a recurring basis and the basis for that measurement, by level within the fair value hierarchy (Note 6):

| | Level 1 | Level 2 | Level 3 |
|---|---|---|---|
| **September 30, 2021** | | | |
| **Financial assets carried at fair value:** | | | |
| Money market funds (1) | $ 28,325 | $ — | $ — |
| | | | |
| **Financial liabilities carried at fair value:** | | | |
| Term loan derivative liability | $ — | $ — | $ 167 |
| | | | |
| **December 31, 2020** | | | |
| **Financial assets carried at fair value:** | | | |
| Money market funds(1) | $ 44,095 | $ — | $ — |
| | | | |
| **Financial liabilities carried at fair value:** | | | |
| Term loan derivative liability | $ — | $ — | $ 196 |

(1) Included in cash and cash equivalents on the Condensed Consolidated Balance Sheets.

The following table represents a roll-forward of the fair value of Level 3 instruments (significant unobservable inputs):

| | September 30, 2021 | December 31, 2020 |
|---|---|---|
| **Financial liabilities** | | |
| Balance at beginning of period | $ 196 | $ 187 |
| Change in fair value of term loan derivative liability | (29) | 9 |
| Balance at end of period | $ 167 | $ 196 |

***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.

***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 the Condensed Consolidated Statements of Operations.

***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 financing. 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 expenses.

***Research and Development Expenses***

All of the Company's research and development 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 clinical research organizations ("CROs") to conduct certain research and development 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 research and development expenses as they are incurred.

***Accrued Research and Development 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 research and development activities. The Company's 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 the Condensed 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.

***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 payments including stock options. The Company's 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 and performance-based vesting and is impacted by the price of its common stock as well as changes in assumptions regarding a number of complex and subjective variables. These variables include 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 is recognized over the period during which an 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. For performance-based vesting, the fair value is also recognized on a straight-line basis over the requisite service period based on whether the performance conditions are probable. The Company reassesses the probability of achieving the performance conditions at each reporting date. 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 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. The Company has 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, 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 equity-settled award.

Prior to the Company's IPO in May 2019, the estimated fair value of the common stock underlying the Company's stock options was determined at each grant date by the Company's board of directors, with input from management. All options to purchase shares of common stock were intended to be exercisable at a price per share not less than the per share fair value of the Company's common stock underlying those options on the date of grant.

In the absence of a public trading market for the Company's common stock prior to the Company's IPO in May 2019, on each grant date, the Company developed an estimate of the fair value of its common stock based on the information known to the Company on the date of grant, upon a review of any recent events and their potential impact on the estimated fair value per share of the common stock and in part on input from an independent third-party valuation. As is provided for in Section 409A of the Internal Revenue Code of 1986, as amended (the "Code"), the Company generally relied on valuations for up to twelve months unless the Company had experienced a material event that would have affected the estimated fair value of its common stock.

The valuations of the Company's common stock performed prior to the Company's IPO in May 2019, were determined in accordance with the guidelines outlined in the American Institute of Certified Public Accountants Practice Aid, Valuation of Privately-Held-Company Equity Securities Issued as Compensation (the "Practice Aid"). The methodology to determine the fair value of common stock included estimating the fair value of the enterprise using a market approach, which estimates the fair value of the Company by including an estimation of the value of the business based on the guideline public companies under a number of different scenarios. The assumptions used to determine the estimated fair value of the Company's common stock were based on numerous objective and subjective factors, combined with management judgment, including external market conditions affecting the pharmaceutical and biotechnology industry and trends within the industry; the Company's stage of development; the rights, preferences and privileges of the Company's convertible preferred stock relative to those of the Company's common stock; the prices at which the Company sold shares of convertible preferred stock; the Company's financial condition and operating results, including the Company's levels of available capital resources; the progress of the Company's research and development efforts; the stage of development and business strategy; the equity market conditions affecting comparable public companies; the general U.S. market conditions and the lack of marketability of the Company's common stock.

The Practice Aid identifies various available methods for allocating enterprise value across classes and series of capital stock to determine the estimated fair value of common stock at each valuation date. In accordance with the Practice Aid, the Company considered the following methods:

- Option Pricing Method ("OPM")—The OPM treats common stock and convertible preferred stock as call options on the total equity value of a company, with exercise prices based on the value thresholds at which the allocation among the various holders of a company's securities changes. Under this method, the common stock has value only if the funds available for distribution to stockholders exceed the value of the liquidation preferences at the time of a liquidity event, such as a strategic sale or merger. The common stock is modeled as a call option on the underlying equity value at a predetermined exercise price. In the model, the exercise price is based on a comparison with the total equity value rather than, as in the case of a regular call option, a comparison with a per share stock price. Thus, common stock is considered to be a call option with a claim on the enterprise at an exercise price equal to the remaining value immediately after the convertible preferred stock liquidation preference is paid. The OPM uses the Black-Scholes option-pricing model to price the call options. This model defines the securities' fair values as functions of the current fair value of a company and uses assumptions, such as the anticipated timing of a potential liquidity event and the estimated volatility of the equity securities.

- Probability Weighted Expected Return Method ("PWERM")—Under the PWERM methodology, the fair value of common stock is estimated based upon an analysis of future values for the company, assuming various outcomes. The common stock value is based on the probability-weighted present value of expected future investment returns considering each of the possible outcomes available as well as the rights of each class of stock. The future value of the common stock under each outcome is discounted back to the valuation date at an appropriate risk-adjusted discount rate and probability weighted to arrive at an indication of value for the common stock.

- Hybrid Method—The hybrid method is a PWERM where the equity value in one of the scenarios is calculated using an OPM. In the hybrid method used by the Company, it considered an IPO as the other potential future liquidity event. The equity value for the IPO scenario was determined using the guideline public company ("GPC"), method under the market approach. The relative probability of the IPO scenario was determined based on an analysis of market conditions at the time and expectations as to the timing and likely prospects of the IPO at each valuation date. In application of the GPC method, the Company considered publicly traded companies in the biopharmaceutical industry that had a similar profile to the Company's as well as recently completed IPOs as indicators of estimated future value in an IPO. The Company then discounted that future value back to the valuation date at an appropriate discount rate.

In determining the estimated fair value of the Company's common stock prior to Company's IPO in May 2019, the board of directors considered the fact that the Company's stockholders could not freely trade the Company's common stock in the public markets. Accordingly, the Company's board of directors applied discounts to reflect the lack of marketability of common stock based on the weighted-average expected time to liquidity. The estimated fair value of the Company's common stock at each grant date reflected a non-marketability discount partially based on the anticipated likelihood and timing of a future liquidity event.

Subsequent to the completion of the Company's IPO in May 2019, the fair value of the Company's common stock has been determined based on the closing price of the Company's common stock as reported on the date of grant on the primary stock exchange on which the Company's common stock is traded.

***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 Condensed 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.

***Leases***

Under ASC 842, *Leases* ("ASC 842"), the Company determines if an arrangement is a lease at its inception. If an operating 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 lease liability at lease commencement. The Company elected the short-term lease practical expedient, therefore, if an operating 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 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 the Company's leases do not provide an implicit rate within the lease, the Company uses its incremental borrowing rate, which is updated periodically, based on information available at the commencement date of the lease to determine the present value of the lease payments.

***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. For all periods presented, shares issuable upon exercise of stock options 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.

***Recently Adopted Accounting Pronouncements***

On January 1, 2021, the Company adopted ASU No. 2019-12-*Income Taxes (Topic 740)*, which simplifies the accounting for income taxes. The adoption of the new guidance did not affect the Company's Condensed Consolidated Financial Statements.

***Recently Issued Accounting Pronouncements***

There have been no new accounting pronouncements during the nine months ended September 30, 2021, which could be expected to materially impact the Company's Condensed Consolidated Financial Statements.

## 3. Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consisted of the following:

| | September 30, 2021 | December 31, 2020 |
|---|---|---|
| Prepaid corporate insurance | $ 1,007 | $ 562 |
| Prepaid other and other current assets | 234 | 373 |
| Prepaid R&D costs | 148 | 333 |
| Total prepaid expenses and other current assets | $ 1,389 | $ 1,268 |

## 4. Leases

Effective March 1, 2013, the Company entered into a lease for office space in New Haven, CT and commencing March 1, 2018, the Company entered into the First Amendment to the lease (collectively, the "Office Space Lease"). The leased space is approximately 5,600 square feet and the Office Space Lease has a term of 60 months. The Office Space Lease requires monthly payments ranging from approximately $10 to $11 through February 1, 2023 and provides for two designated months of free rent.

The incremental borrowing rate used on 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 new leases during the nine months ended September 30, 2021.

The Office Space Lease is an operating lease and the remaining term as of September 30, 2021 is approximately 1.5 years. The Company has no financing leases. The following table summarizes the Company's operating lease as presented on its Condensed Consolidated Balance Sheets:

| | September 30, 2021 | December 31, 2020 |
|---|---|---|
| *Assets:* | | |
| Operating lease right-of-use asset | $ 156 | $ 227 |
| *Liabilities:* | | |
| Operating lease liabilities, current portion | 116 | 113 |
| Operating lease liabilities, long term portion | 58 | 144 |
| Total operating lease liabilities | $ 174 | $ 257 |

Future minimum lease payments from September 30, 2021 until the expiration of the operating leases are as follows:

| | |
|---|---|
| 2021 | $ 34 |
| 2022 | 131 |
| 2023 | 24 |
| Total lease payments | 189 |
| Less: imputed discount rate | (15) |
| Carrying value of operating lease liabilities | $ 174 |

Lease expense under operating leases, including leases of office equipment, was $29 and $31 for the three months ended September 30, 2021 and 2020, respectively and $90 and $93 for the nine months ended September 30, 2021 and 2020, respectively. Lease payments made in the three months ended September 30, 2021 and 2020 were $35 and $23, respectively and $104 and $103 for the nine months ended September 30, 2021 and 2020, respectively, with such amounts reflected in the Condensed Consolidated Statements of Cash Flows in operating activities.

## 5. Accrued Expenses

Accrued expenses consisted of the following:

| | September 30, 2021 | December 31, 2020 |
|---|---|---|
| Accrued R&D projects | $ 1,660 | $ 1,754 |
| Accrued compensation and benefits | 960 | 954 |
| Accrued consulting and professional fees | 624 | 560 |
| Accrued other | 70 | 158 |
| Total accrued expenses | $ 3,314 | $ 3,426 |

## 6. Debt

***SVB Term Loan***

On August 13, 2020 (the "Effective Date"), the Company entered into a loan and security agreement (the "SVB Loan Agreement") with 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 Company may use the proceeds from the SVB Term Loan for working capital and general corporate purposes. The SVB Term Loan bears 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 receives evidence satisfactory to it that the Company has (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 will be 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). On the first business day of each month, the Company will be required to make monthly interest payments and commencing on March 1, 2022, the Company will be 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 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 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 the Company's properties, rights and assets, except for its intellectual property (which is 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 modifies the conditions under which the Company is required to cash collateralize all outstanding amounts owed to SVB under the SVB Loan Agreement. Under the Loan Amendment, if the Company fails 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 will be required to deposit unrestricted and unencumbered cash equal to 100% of the principal amount of the SVB Term Loan then outstanding in a cash collateral account with SVB, which can be used by SVB to prepay the SVB Term Loan at any time. In addition, the Loan Amendment provides that if the Company fails 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 Company will be 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 Sales Agreement and two private placements, which took place in October 2021 (see Note 12).

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 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.

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 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 amortized over the remaining life of the SVB Term Loan using the effective interest method. Amortization of these deferred financing charges totaled $11 and $22 for the three and nine months ended September 30, 2021, respectively and is included in interest expense in the Company's Condensed Consolidated Statements of Operations. The unamortized deferred charges totaled $93 and $48 at September 30, 2021 and December 31, 2020, respectively and are included as a direct reduction of the carrying value of the term loan payable on the Company's Condensed 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 included as a reduction in the balance of the term loan payable on the Company's Condensed Consolidated Balance Sheets and will be accreted over the life of the SVB Term Loan using the effective interest method. Accretion of these loan discounts totaled $3 and $8 for the three and nine months ended September 30, 2021

and is included in interest expense in the Company's Condensed Consolidated Statements of Operations. At September 30, 2021 and December 31, 2020, the loan discount-financing costs balance was $15 and $23, respectively.

In connection with the SVB Loan Agreement, the Company is 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 accrued over the life of the SVB Term Loan using the effective interest method and is included as an increase in the balance of the term loan payable on the Company's Condensed Consolidated Balance Sheets. At September 30, 2021 and December 31, 2020, $538 and $183 was accrued for the final payment fee, respectively.

Upon the occurrence of the Phase 3 Event, the interest rate on the SVB Term Loan will increase by 2.00% (the "Contingent Interest Rate Increase") as described above. The Contingent Interest Rate Increase represents 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 adjusts this liability to fair value at each reporting date it remains outstanding, with such adjustments recorded as non-cash charges in other (expense) income, net in the Company's Condensed Consolidated Statements of Operations. The total fair value of this liability was determined to be $167 and $196 at September 30, 2021 and December 31, 2020, respectively. The change in fair value of the term loan derivative liability as of September 30, 2021 as compared to the fair value at December 31, 2020 was $29. The term loan derivative liability is presented as a current liability on the Company's Condensed Consolidated Balance Sheets as of September 30, 2021 and as a non-current liability as of December 31, 2020. Upon recording such term loan derivative liability, the Company also recorded an offsetting term loan discount – interest, to be amortized to interest expense in the Company's Condensed Consolidated Statements of Operations through the SVB Term Loan's maturity date using the effective interest method. Such amortization was $19 and $56 in the three and nine months ended September 30, 2021, respectively. At September 30, 2021 and December 31, 2020, the balance of the term loan discount – interest was $102 and $158, respectively and is included as a reduction in the balance of the term loan payable on the Company's Condensed Consolidated Balance Sheets.

Fair values of the term loan derivative liability are estimated utilizing a probability-weighted cash flow approach, including variables for the timing of the Phase 3 Event and other probability estimates. For the fair value calculations of the term loan derivative liability at September 30, 2021 and December 31, 2020, significant inputs included the Contingent Interest Rate Increase of 2.00%, a discount rate of 12.0% and the SVB Term Loan maturity date of February 1, 2024.

As of September 30, 2021, the Company had outstanding borrowings of $14.0 million under the SVB Term Loan and the term loan payable balance as presented on the Company's Condensed Consolidated Balance Sheets as of September 30, 2021 and December 31, 2020 was comprised as shown below.

| | September 30, 2021 | December 31, 2020 |
|---|---|---|
| Principal outstanding under term loan | $ 14,000 | $ 14,000 |
| Term loan discount-interest | (102) | (158) |
| Term loan discount-unamortized deferred charges | (93) | (48) |
| Term loan discount-financing costs, net of accretion | (15) | (23) |
| Term loan-final payment fee | 538 | 183 |
| | 14,328 | 13,954 |
| Less current portion | 4,083 | - |
| Term loan payable, non-current | $ 10,245 | $ 13,954 |

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 three and nine months ended September 30, 2021 and 2020, respectively.

| | Three Months Ended September 30, | | Nine Months Ended September 30, | |
|---|---|---|---|---|
| | 2021 | 2020 | 2021 | 2020 |
| Interest payments | $ 152 | $ 80 | $ 451 | $ 80 |
| Accretion and amortization of term loan discounts | 33 | 4 | 87 | 4 |
| Accrual of the final payment fee | 118 | 64 | 355 | 64 |
| | $ 303 | $ 148 | $ 893 | $ 148 |

## 7. Stockholders' Equity

As of September 30, 2021 and December 31, 2020, the Company had reserved shares of common stock for the exercise of outstanding stock options and shares of common stock remaining available for future stock-based awards under the Company's 2012 Stock Incentive Plan, 2019 Stock Incentive Plan and 2019 Employee Stock Purchase Plan, as shown in the table below:

| | September 30, 2021 | December 31, 2020 |
|---|---|---|
| Shares of common stock reserved for future issuance under the 2012 Stock Incentive Plan | 761,553 | 921,824 |
| Shares of common stock reserved for future issuance under the 2019 Stock Incentive Plan | 3,299,064 | 2,396,922 |
| Shares of common stock reserved for future issuance under the 2019 Employee Stock Purchase Plan | 503,789 | 327,454 |
| | 4,564,406 | 3,646,200 |

***Private Placements***

On October 5, 2021 and October 18, 2021, the Company issued common stock and warrants to purchase common stock in two private placements (the "October 2021 Private Placements"). Refer to Note 12 for additional information.

***At-the-Market Offering***

In June 2020, the Company entered into the ATM Sales Agreement, under which the Company may issue and sell shares of its common stock, from time to time, having an aggregate offering price of up to $12.0 million. Sales of common stock under the ATM Sales Agreement may be made 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 ATM Sales Agreement. The Company began making sales pursuant to the ATM Sales Agreement in July 2020. During the three and nine months ended September 30, 2021, the Company issued and sold an aggregate of 162,026 and 2,895,518 shares of common stock, respectively, for gross proceeds of $0.3 million and $7.7 million, respectively, before deducting estimated commissions and allocated fees of less than $0.1 million and $0.6 million, respectively. As of September 30, 2021, the Company had issued and sold an aggregate of 3,583,394 shares of common stock for gross proceeds of $10.9 million, before deducting estimated commissions and allocated fees of $0.8 million. Under the terms of the October 2021 Private Placements, as described in Note 12, the Company agreed not to issue or sell additional shares under the ATM Sales Agreement on or prior to January 4, 2022.

***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 that, subject to the terms and conditions therein, the Company has 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 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 of the shares sold will be based on the market prices prevailing immediately preceding the time of sale as computed under the LPC Purchase Agreement. 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, the Company agreed to not issue or sell additional shares under the LPC Purchase Agreement on or prior to April 6, 2023.

***Stock-Based Awards***

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 4,060,617 as of September 30, 2021, of which 1,011,437 shares remained available for grant under the 2019 Plan. 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) equal to the number of shares of the Company's common stock subject to outstanding awards under the 2012 Stock Incentive Plan (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 lesser 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, 2021 and January 1, 2020, respectively, the number of shares reserved for issuance under the 2019 Plan increased pursuant to the terms of the 2019 Plan by an additional 741,871 shares and 713,383 shares, equal to 4% of the Company's then-outstanding common stock.

The 2012 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.

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. As of September 30, 2021 and December 31, 2020, respectively, options to purchase 2,287,627 shares and 1,249,653 shares of common stock were granted and outstanding, net of cancellations, under the 2019 Plan. As of September 30, 2021 and December 31, 2020, options to purchase 761,553 and 921,824 shares of common stock, respectively, were granted and outstanding, net of cancellations, under the 2012 Plan.

In April 2019, the Company's board of directors adopted a resolution effective on May 7, 2019, that no further stock options or other equity-based awards may be granted under the 2012 Plan.

In February 2021, the compensation committee of the Company's board of directors approved the grant of stock options with performance-based vesting ("PSOs") to employees of the Company. The PSOs granted in February 2021, 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 nine months ended September 30, 2021 is as follows:

| | Number of Option Shares | | Weighted Average Exercise Price |
|---|---|---|---|
| Outstanding as of December 31, 2020 | 2,171,477 | $ | 5.62 |
| Granted | 1,474,875 | $ | 2.94 |
| Forfeited | (420,241) | $ | 4.39 |
| Expired | (176,931) | $ | 6.30 |
| Exercised | — | $ | — |
| Outstanding as of September 30, 2021 | 3,049,180 | $ | 4.45 |
| Options exercisable as of September 30, 2021 | 1,304,796 | $ | 5.02 |
| Options unvested as of September 30, 2021 | 1,744,384 | $ | 4.03 |

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 Plan was 518,918 as of September 30, 2021, of which 503,789 shares remain available for issuance. 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, 2021 and January 1, 2020, 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 185,467 shares and 178,345 shares, equal to 1% of the Company's then-outstanding common stock.

All of the Company's employees are eligible to participate in the 2019 ESPP, provided that:

- such person is customarily employed by the Company for more than 20 hours a week and for more than five months in a calendar year;
- such person has been employed by the Company for at least three months prior to enrolling in the 2019 ESPP; and
- such person was an employee of the Company on the first day of the applicable offering period under the 2019 ESPP.

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 Condensed Consolidated Statements of Operations:

| | Three Months Ended September 30, | | Nine Months Ended September 30, | |
|---|---|---|---|---|
| | 2021 | 2020 | 2021 | 2020 |
| Research and development expense | $ 169 | $ 82 | $ 593 | $ 259 |
| General and administrative expense | 371 | 506 | 1,410 | 1,648 |
| | $ 540 | $ 588 | $ 2,003 | $ 1,907 |

## 8. Income Taxes

During the three and nine months ended September 30, 2021 and 2020, the Company maintained a full valuation allowance on deferred tax assets. The amounts recorded for income tax (expense) benefit during the three and nine months ended September 30, 2021 and 2020, were to align the Company's estimates for its state research and development credits in each given year.

## 9. 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:

| | Three Months Ended September 30, | | Nine Months Ended September 30, | |
|---|---|---|---|---|
| | 2021 | 2020 | 2021 | 2020 |
| Net loss | $ (7,255) | $ (7,378) | $ (25,420) | $ (23,235) |
| Weighted average common shares used in net loss per share attributable to common stockholders, basic and diluted | 21,607,979 | 18,134,886 | 20,390,852 | 17,935,865 |
| Basic and diluted net loss per common share outstanding | $ (0.34) | $ (0.41) | $ (1.25) | $ (1.30) |

The Company's potential dilutive securities, which include stock options, 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 common shares underlying stock options, based on stock options outstanding as of September 30, 2021 and 2020, were excluded from the calculations of diluted net loss per share attributable to common stockholders for the periods indicated because including them would have had an anti-dilutive effect.

## 10. 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. ("Penwest") (subsequently merged into its parent, Endo Pharmaceuticals Inc. ("Endo")) for an exclusive worldwide sublicensable license under certain patent rights and know-how controlled by Penwest 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 Penwest a non-creditable, minimal 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, such as the Phase 2b/3 PRISM trial and $0.8 million, which would become due upon the marketing approval of a licensed product in the U.S. and to pay mid-single-digit 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.

***Exclusive License Agreement with Rutgers***

In November 2018, the Company entered into an agreement with Rutgers, The State University of New Jersey ("Rutgers") for an exclusive, worldwide, sublicensable license under certain patent rights controlled by Rutgers and for a non-exclusive, worldwide, sublicensable license under certain know-how controlled by Rutgers, in each case to develop and commercialize products incorporating nalbuphine for any human or animal use.

Upon entering into the license agreement, the Company paid Rutgers a minimal upfront license issue fee, which was recorded as R&D expense in 2018 and agreed to pay Rutgers a minimal annual license fee. The Company may become obligated to make milestone payments to Rutgers in the aggregate of up to $0.3 million based on the achievement of certain clinical, regulatory and sales milestones. The Company has also agreed to pay Rutgers a low single-digit percentage of certain income it receives from sublicensees and to pay tiered low single-digit royalties based on net sales of licensed products by the Company, its affiliates and sublicensees.

The Company's royalty obligation with respect to each licensed product in each country commences on the date of the first commercial sale of the licensed product in that country following receipt of marketing approval and extends until the later of the date of expiration, unenforceability or invalidation of the last valid claim of any licensed patent or patent application covering the licensed product in the country and 10 years after the first commercial sale of the first licensed product sold anywhere in the world, which period is referred to as the royalty term. Upon the expiration of the royalty term for a licensed product in a country, the license granted to the Company under the agreement shall become perpetual, fully paid-up, irrevocable and royalty-free in such country. The royalty is subject to reduction in certain circumstances.

In June 2021, the Company entered into an amendment with Rutgers to extend the deadline to commence a clinical trial on nalbuphine ER for LID to December 31, 2022. The Company paid a minimal fee related to this amendment, which was recorded as R&D expense during the second quarter of 2021.

***Restructuring Agreement with MentiNova, LLC***

In November 2018, concurrent with the signing of the agreement with Rutgers described above, the Company entered into a restructuring agreement with MentiNova, LLC ("MentiNova"), for the purchase of specified information and know-how, specified contractual rights and benefits and all books and records of MentiNova related thereto (collectively, the "Acquired Assets").

Upon entering into the license agreement, the Company paid MentiNova an aggregate upfront payment of $0.1 million, which was recorded as R&D expense in 2018, subject to specified closing adjustments. The Company may become obligated to make milestone payments to MentiNova in the aggregate of up to $1.2 million based on the achievement of certain clinical and regulatory milestones as well as tiered low single-digit royalties based on net sales of products containing nalbuphine as the sole active pharmaceutical ingredient that are developed by the Company using the Acquired Assets or the intellectual property licensed to the Company under the Rutgers agreement described above (the "Rutgers IP") for indications that are within the scope of the Rutgers IP. The royalty is subject to reduction in certain circumstances.

**11. 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 clinical trials and 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 4 and Note 10).

**12. Subsequent Events**

***Financing***

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 has an exercise price of $0.001 per share, became exercisable immediately upon issuance and will continue to be 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.

**Item 2. 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 Condensed Consolidated Financial Statements and related notes appearing elsewhere in this Quarterly Report on Form 10-Q and our audited consolidated financial statements and related notes for the year ended December 31, 2020 included in our Annual Report on Form 10-K, filed with the Securities and Exchange Commission, or SEC, on March 25, 2021. Some of the statements contained in this discussion and analysis or set forth elsewhere in this Quarterly Report on Form 10-Q, 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 Quarterly Report on Form 10-Q, particularly including those risks identified in Part II-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 Quarterly Report on Form 10-Q. Statements made herein are as of the date of the filing of this Quarterly Report on Form 10-Q 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 Quarterly Report on Form 10-Q, 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 (nalbuphine ER) to treat serious neurologically mediated conditions. We are developing Haduvio for the treatment of chronic pruritus associated with prurigo nodularis and chronic cough in patients with idiopathic pulmonary fibrosis, or IPF. We are also developing Haduvio in levodopa-induced dyskinesia, or LID, in patients with Parkinson's disease.

We are conducting a Phase 2b/3 clinical trial of Haduvio, which we refer to as the Phase 2b/3 PRISM trial, in patients with severe pruritus associated with prurigo nodularis. The Phase 2b/3 PRISM trial is a randomized, double-blind, placebo controlled, two-arm treatment study that is designed to evaluate the safety and anti-pruritic efficacy of Haduvio in patients in the United States, or U.S., and Europe. In accordance with the protocol for the Phase 2b/3 PRISM trial, we conducted a sample size re-estimation, or SSRE, analysis in July 2020, following such time as approximately 45% of the initial targeted number of subjects in the trial were evaluable for the primary endpoint. Based on the analysis, the independent Data Monitoring Committee, or DMC, recommended that the Phase 2b/3 PRISM trial should continue and that the trial size should increase from an initial enrollment target of 240 to 360 subjects, which maintains the statistical power for the primary endpoint. Based on the DMC's recommendation, we have increased the planned trial size to 360 subjects. The pace of enrollment in the trial was impacted by the pandemic caused by the novel coronavirus, or COVID-19, which pandemic we refer to as the COVID-19 pandemic, as new subject screening and most subject enrollment were temporarily halted in March 2020. Our sites began to restart subject screening and enrollment during May and June 2020. We currently have more than 60 active sites globally and approximately 90% of the planned 360 subjects have enrolled in the trial. Subject to the uncertainties associated with the COVID-19 pandemic, we expect to report top-line data in the first half of 2022. If the Phase 2b/3 PRISM trial is successful, we expect that we will use the Phase 2b/3 PRISM trial and an additional Phase 3 clinical trial that we believe we will need to conduct to support the submission of a new drug application , or NDA, to the U.S. Food and Drug Administration, or 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 pruritus associated with prurigo nodularis.

We are also conducting a Phase 2 clinical trial of Haduvio for chronic cough in patients with IPF, which we refer to as the Phase 2 CANAL trial. The Phase 2 CANAL trial is a 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 chronic cough in patients with IPF. This trial is designed to enroll approximately 60 subjects with a goal to have 44 study completers. We are conducting the trial at multiple sites in the U.K. Due to the COVID-19 pandemic and the specific at-risk nature of IPF patients, our clinical sites had previously halted their enrollment and treatment of subjects in this trial in March 2020. While subject screening and enrollment resumed at certain clinical trial sites in the fourth quarter of 2020, all sites in the trial paused screening again in December 2020, in response to a shelter-in-place directive from the U.K. government. This shelter-in-place directive expired in March 2021, and the remaining COVID-19 pandemic related restrictions were lifted in July 2021. The U.K. government may choose to reinstate any and/or all of the restrictions in the future depending on COVID-19 infection rates. Screening activity has resumed and is steadily progressing at most sites following the lifting of the shelter-in-place directive. However, we expect that some sites may take longer to resume their trial activity as the clinical research related infrastructure was disrupted by the COVID-19 pandemic and that other sites may cease to participate in the trial entirely. Subject to the uncertainties associated with the COVID-19 pandemic related restrictions in the U.K., we expect to report top-line data for this trial in the first half of 2022.

With respect to LID, we have written the protocol for a Phase 2 clinical trial for LID in patients with Parkinson's disease. We plan to determine next steps in the program once we complete the Phase 2b/3 PRISM and Phase 2 CANAL trials.

We are currently focusing our financial and operational resources on completing the Phase 2b/3 PRISM and the Phase 2 CANAL trials. After we receive top-line data from both of these trials, we will evaluate additional indications for which we may choose to pursue the development of Haduvio.

Since commencing operations in 2011, we have devoted substantially all 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 September 30, 2021, we had an accumulated deficit of $172.4 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 pruritus associated with prurigo nodularis, chronic cough in patients with IPF or LID in patients with Parkinson's disease and we can provide no assurance that we will ever generate revenue or profits.

In June 2020, we entered into an at-the-market Sales Agreement with SVB Leerink LLC, or SVB Leerink, which we refer to as the ATM Sales Agreement, under which we may issue and sell shares of common stock, from time to time, having an aggregate offering price of up to $12.0 million. Sales of common stock under the ATM Sales Agreement may be made by any method that is deemed an "at-the-market" offering as defined in Rule 415(a)(4) under the Securities Act of 1933, or the Securities Act, as amended. We are 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 September 30, 2021, we had issued and sold an aggregate of 3,583,394 shares of

common stock for gross proceeds of $10.9 million, before deducting estimated commissions and allocated fees of $0.8 million. Under the terms of the October 2021 Private Placements, as described below, we agreed to not issue and sell additional shares under the ATM Sales Agreement on or prior to January 4, 2022.

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, we are required to make monthly interest payments and commencing on March 1, 2022, we will be 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, we and SVB entered into an amendment to the SVB Loan Agreement, which we refer to as the Loan Amendment, that modified the conditions under which we will 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 Amendment, 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 has an exercise price of $0.001 per share, became exercisable immediately upon issuance and will continue to be exercisable until exercised in full. Of the accompanying common stock warrants, warrants to purchase an aggregate of 9,151,122 shares will expire in April 2025 and warrants to purchase an aggregate of 9,151,122 shares will 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 September 30, 2021, we had cash and cash equivalents of $29.3 million and in October 2021 we received approximately $14.8 million in gross proceeds from the October 2021 Private Placements. We believe that our existing cash and cash equivalents will not enable us to fund our operating expenses and capital expenditure requirements for 12 months from the date of issuance of the Condensed Consolidated Financial Statements included in this Quarterly Report on Form 10-Q. After considering various risks and uncertainties as prescribed by Accounting Standards Update No. 2014-15, *Disclosures of Uncertainties about an Entity's Ability to Continue as a Going Concern (Subtopic 205-40)*, we concluded that there is substantial doubt about our ability to continue as a going concern as of the date of issuance of the Condensed Consolidated Financial Statements included in this Quarterly Report on Form 10-Q without additional capital. We have based our estimate as to how long we expect our existing cash and cash equivalents to continue to fund our operations on assumptions that may prove to be wrong and we could use our available capital resources sooner than we expect. See "—Liquidity and Capital Resources." Our future viability beyond that point is dependent on our ability to raise additional capital to finance our operations.

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 our ongoing Phase 2b/3 PRISM trial in patients with pruritus associated with prurigo nodularis and the additional Phase 3 clinical trial we believe we will be required to conduct to support the submission of an NDA to the FDA for Haduvio for the treatment of pruritus associated with prurigo nodularis, our ongoing Phase 2 CANAL trial in chronic cough in patients with IPF, the development and validation of our commercial manufacturing process for Haduvio and other development activities, including potentially commencing Phase 2 clinical trials for the treatment of LID in patients with Parkinson's disease. In addition, we may continue to incur additional expenses as a result of the COVID-19 pandemic and related clinical trial delays and interruptions.

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. We have experienced restrictions and delays at our existing clinical sites. For example, in our ongoing Phase 2b/3 PRISM trial, new subject screening and most enrollment was temporarily halted due to the COVID-19 pandemic in March 2020. Many of our sites restarted subject screening and enrollment throughout May and June 2020. Furthermore, multiple sites in the Phase 2b/3 PRISM trial required some remote monitoring of subject data, although all sites have

now re-opened for in-person monitoring visits. 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. In addition, the clinical sites in our ongoing Phase 2 CANAL trial temporarily suspended 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. While subject screening and enrollment for our Phase 2 CANAL trial resumed at certain clinical trial sites in the fourth quarter of 2020, all sites in the trial paused screening again in December 2020 in response to a shelter-in-place directive from the U.K. government. This shelter-in-place directive expired in March 2021 and the other COVID-19 pandemic related restrictions were lifted in July 2021. The U.K. government may choose to reinstate any and/or all of the restrictions in the future depending on COVID-19 infection rates. Screening activity has resumed and is steadily progressing at most sites following the lifting of the shelter-in-place directive. However, we expect that some sites may take longer to resume their trial activity as the clinical research related infrastructure was disrupted by the COVID-19 pandemic and that other sites may cease to participate in the trial entirely. The COVID-19 pandemic 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 outbreak, 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 or travel restrictions 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 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 have taken temporary precautionary measures intended to help minimize the risk of the virus to our employees, including allowing employees to work remotely part of the week and suspending non-essential travel worldwide for our employees.

**Components of Operating Results**

***Operating Expenses***

*Research and Development Expenses*

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 clinical 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, whether as a result of the COVID-19 pandemic or otherwise, 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 (Expense) Income, Net***

*Change in Fair Value of Term Loan Derivative Liability*

In connection with the SVB Term Loan, upon the occurrence of the Phase 3 Event, the interest rate on the SVB Term Loan will increase by 2.00%. For further discussion of the Phase 3 Event, see “Interest Expense”. This contingent interest rate increase

represents 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 adjust this liability to fair value at each reporting date it remains outstanding. We recognized changes in the fair value of this term loan derivative in our statements of operations as a component of other (expense) income, net.

*Other Expense*

Other expense consists 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 with Lincoln Park in June 2021.

*Interest Income*

Interest income consists of interest earned from money market funds on our cash and cash equivalents.

*Interest Expense*

In August 2020, we entered into the SVB Loan Agreement under which we borrowed $14.0 million under a term loan or the SVB Term Loan. In connection with the SVB Term Loan, we recognize interest expense which includes 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. The SVB Term Loan bears 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 receives evidence satisfactory to it that we have (i) received positive data for the Phase 2b/3 PRISM trial sufficient to advance Haduvio into a second Phase 3 clinical trial for chronic pruritus associated with 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 will be adjusted to a floating rate equal to the greater of (A) the prime rate plus 3.00% and (B) 6.25%. The SVB Term Loan requires interest-only payments until March 2022. We will then be 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.

**Results of Operations**

***Comparison of the Three Months Ended September 30, 2021 and 2020***

The following table summarizes our results of operations for the periods indicated (in thousands):

| | Three Months Ended September 30, | | |
|---|---|---|---|
| | 2021 | 2020 | Change |
| Operating expenses: | | | |
| Research and development | $ 4,718 | $ 4,828 | $ (110) |
| General and administrative | 2,229 | 2,416 | (187) |
| Total operating expenses | 6,947 | 7,244 | (297) |
| Loss from operations | (6,947) | (7,244) | 297 |
| Other (expense) income: | | | |
| Change in fair value of term loan derivative liability | (5) | — | (5) |
| Interest income | 2 | 3 | (1) |
| Interest expense | (303) | (148) | (155) |
| Total other expense, net | (306) | (145) | (161) |
| Loss before income taxes | (7,253) | (7,389) | 136 |
| Income tax (expense) benefit | (2) | 11 | (13) |
| Net loss | $ (7,255) | $ (7,378) | $ 123 |

***Operating Expenses***

*Research and Development Expenses*

The following table summarizes our research and development expenses for the periods indicated (in thousands):

| | Three Months Ended September 30, | | |
|---|---|---|---|
| | 2021 | 2020 | Change |
| Clinical development expenses | $ 3,175 | $ 3,683 | $ (508) |
| Personnel and related expenses | 1,018 | 704 | 314 |
| Consulting expenses and professional fees | 377 | 334 | 43 |
| Stock-based compensation expenses | 91 | 82 | 9 |
| Other research and development expenses | 57 | 25 | 32 |
| Total research and development expenses | $ 4,718 | $ 4,828 | $ (110) |

Research and development expenses for the three months ended September 30, 2021 decreased to $4.7 million from $4.8 million for the corresponding period in 2020, primarily due to decreased purchases of clinical trial supplies. This decrease was partially offset by an increase in personnel-related expenses as a result of an increase in our employee headcount. For the periods presented, all of our research and development expenses related to our development activity for Haduvio.

*General and Administrative Expenses*

General and administrative expenses for the three months ended September 30, 2021 decreased to $2.2 million from $2.4 million for the corresponding period in 2020. The decrease was primarily due to decreased market research costs as well as lower stock-based compensation expense as a result of employee terminations, which were partially offset by higher legal and other professional fees.

*Other Expense, Net*

Other expense, net for the three months ended September 30, 2021 was $0.3 million compared to $0.1 million for the corresponding period in 2020. This change was primarily due to a $0.2 million increase in interest expense due to a full quarter's recognition of interest expense on the SVB Term Loan as the SVB Term Loan was entered into in August 2020.

***Comparison of the Nine Months Ended September 30, 2021 and 2020***

The following table summarizes our results of operations for the periods indicated (in thousands):

| | Nine Months Ended September 30, | | |
|---|---|---|---|
| | 2021 | 2020 | Change |
| Operating expenses: | | | |
| Research and development | $ 16,805 | $ 15,768 | $ 1,037 |
| General and administrative | 7,398 | 7,528 | (130) |
| Total operating expenses | 24,203 | 23,296 | 907 |
| Loss from operations | (24,203) | (23,296) | (907) |
| Other (expense) income: | | | |
| Change in fair value of term loan derivative liability | 29 | — | 29 |
| Other expense | (375) | — | (375) |
| Interest income | 7 | 174 | (167) |
| Interest expense | (893) | (148) | (745) |
| Total other (expense) income, net | (1,232) | 26 | (1,258) |
| Loss before income taxes | (25,435) | (23,270) | (2,165) |
| Income tax benefit | 15 | 35 | (20) |
| Net loss | $ (25,420) | $ (23,235) | $ (2,185) |

***Operating Expenses***

*Research and Development Expenses*

The following table summarizes our research and development expenses for the periods indicated (in thousands):

| | Nine Months Ended September 30, | | |
|---|---|---|---|
| | 2021 | 2020 | Change |
| Clinical development expenses | $ 11,223 | $ 12,453 | $ (1,230) |
| Personnel and related expenses | 3,460 | 2,104 | 1,356 |
| Consulting expenses and professional fees | 1,375 | 850 | 525 |
| Stock-based compensation expenses | 593 | 259 | 334 |
| Other research and development expenses | 154 | 102 | 52 |
| Total research and development expenses | $ 16,805 | $ 15,768 | $ 1,037 |

Research and development expenses for the nine months ended September 30, 2021 increased to $16.8 million from $15.8 million for the corresponding period in 2020, primarily due to an increase in personnel-related expenses as a result of an increase in our employee headcount, including an increase in stock-based compensation associated with the increase in employee headcount. Consulting and professional fees were also higher. These increases were partially offset by decreased clinical development expenses related to decreased purchases of clinical trial supplies and decreased expenses reflecting the completion of our Phase 1b clinical trial in patients with chronic liver disease in the first half of 2020. These decreased clinical development expenses were partially offset by increased costs associated with increased activity and enrollment in our ongoing Phase 2b/3 PRISM trial. For the periods presented, all of our research and development expenses related to our development activity for Haduvio.

*General and Administrative Expenses*

General and administrative expenses for the nine months ended September 30, 2021 decreased to $7.4 million from $7.5 million for the corresponding period in 2020. The decrease was primarily due to decreased market research costs as well as lower stock-based compensation expense as a result of employee terminations, which were partially offset by higher legal and other professional fees.

*Other (Expense) Income, Net*

Other (expense) income, net for the nine months ended September 30, 2021 was an expense of $1.2 million compared to income of less than $0.1 million for the corresponding period in 2020. This change was primarily due to a $0.7 million increase in interest expense due to a full nine months of recognition of interest expense on the SVB Term Loan as the SVB Term Loan was entered into in August 2020, as well as an increase of $0.4 million related to 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. Also contributing to the change was a decrease in interest income of $0.2 million, primarily due to lower market interest rates and lower average cash balances.

**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 initial public offering, or the 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 with Solar Capital, Ltd. and Square 1 Bank, or the Solar 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 the Solar Term Loan. As of June 30, 2018, all amounts owed under the Solar Term Loan had been paid in full.

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 issue and sell shares of common stock, from time to time, having an aggregate offering price of up to $12.0 million. Sales of common stock under the ATM Sales Agreement may be made by any method that is deemed an "at-the-market" offering as defined in Rule 415(a)(4) under the Securities Act. We are 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 September 30, 2021 we had issued and sold an aggregate of 3,583,394 shares of common stock for gross proceeds of $10.9 million, before deducting estimated commissions and allocated fees of $0.8 million. Under the terms of the October 2021 Private Placements, we agreed to not issue or sell additional shares under the ATM Sales Agreement on or prior to January 4, 2022.

***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. The proceeds from the SVB Term Loan may be used by us for working capital and general corporate purposes. The SVB Term Loan bears 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 receives evidence satisfactory to it that we have (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 will be adjusted to a floating rate equal to the greater of (A) the prime rate plus 3.00% and (B) 6.25%. On the first business day of each month, we are required to make monthly interest payments and commencing on March 1, 2022, we will be 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.

On July 6, 2021, we and SVB entered into the Loan Amendment. The Loan Amendment modifies the conditions under which we are required to cash collateralize outstanding amounts owed to SVB under the SVB Loan Agreement. Under the Loan Amendment, if we fail to receive positive data in our Phase 2b/3 PRISM trial or, prior to June 30, 2022, fail 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 will be required to deposit unrestricted and unencumbered cash equal to 100% of the principal amount of the SVB Term Loan then outstanding in a cash collateral account with SVB, which can be used by SVB to prepay the SVB Term Loan at any time. In addition, the Loan Amendment provides that if we fail to maintain at least $20.0 million in unrestricted and unencumbered cash in our accounts with SVB at any time prior to the satisfaction of all the Milestone Conditions, we will be 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.

***Private Placements***

On October 5, 2021 and October 18, 2021, we issued and sold in two 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 has an exercise price of $0.001 per share, became exercisable immediately upon issuance and will continue to be exercisable until exercised in full. Of the accompanying common stock warrants, warrants to purchase an aggregate of 9,151,122 shares will expire in April 2025 and warrants to purchase an aggregate of 9,151,122 shares will expire in October 2028. The accompanying common stock warrants have an exercise price of $1.37 per share and became exercisable immediately upon issuance.

***Equity Purchase 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 that, subject to the terms and conditions set forth therein, we have the right, but not the obligation, to sell to Lincoln Park and Lincoln Park is 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 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 of the October 2021 Private Placements, we agreed to not issue or sell additional shares under the LPC Purchase Agreement on or prior to April 6, 2023.

***Cash Flows***

As of September 30, 2021, we had cash and cash equivalents of $29.3 million. Our cash and cash equivalents are primarily held in money market accounts. The following table summarizes our cash flows for each of the periods presented below (in thousands):

| | Nine Months Ended September 30, | | |
|---|---|---|---|
| | 2021 | 2020 | Change |
| Net cash used in operating activities | $ (22,717) | $ (20,076) | $ (2,641) |
| Net cash used in investing activities | — | (27) | 27 |
| Net cash provided by financing activities | 7,034 | 16,083 | (9,049) |
| Net decrease in cash and cash equivalents | $ (15,683) | $ (4,020) | $ (11,663) |

*Operating Activities*

During the nine months ended September 30, 2021, operating activities used $22.7 million of net cash, resulting from our net loss of $25.4 million and net changes in our operating assets and liabilities of $0.1 million, partially offset by non-cash charges of $2.8 million. The non-cash charges consisted primarily of stock-based compensation expense of $2.0 million, $0.4 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. Changes in our operating assets and liabilities consisted of a $0.2 million decrease in accrued expenses and other liabilities, a $0.1 million increase in prepaid expenses and other current assets and a $0.2 million increase in accounts payable. 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 and decreased accruals related to non-income based taxes, partially offset by an increase in accrued consulting and professional fees. The increase in prepaid expenses and other current assets was primarily due to an increase in prepayments of our corporate insurance policies. The increase in accounts payable was primarily due to the timing of vendor invoices.

During the nine months ended September 30, 2020, operating activities used $20.1 million of cash, resulting from our net loss of $23.2 million, partially offset by changes in our operating assets and liabilities of $1.2 million, net and non-cash charges of $2.0 million. Changes in our operating assets and liabilities for the nine months ended September 30, 2020 consisted of a $1.2 million increase in accrued expenses, a $0.3 million decrease in accounts payable and a $0.3 million decrease in prepaid expenses and other current assets. The increase in accrued expenses was primarily due to increased accruals for research, development and clinical trial work performed by our CROs and increased accruals related to professional fees. The decrease in accounts payable was primarily due to the timing of vendor invoices. The decrease in prepaid expenses and other current assets was primarily due to a refund of prepayments made to one of our vendors, which we received in the first quarter of 2020, partially offset by increases in prepaid expenses due to prepayments of our corporate insurance policies. The non-cash charges for the nine months ended September 30, 2020 consisted primarily of stock-based compensation expense of $1.9 million.

*Investing Activities*

During the nine months ended September 30, 2021 and 2020, we used an insignificant amount of cash in investing activities.

*Financing Activities*

During the nine months ended September 30, 2021, net cash provided by financing activities was $7.0 million, primarily consisting of gross cash proceeds of $7.7 million from sales of our common stock under the ATM Sales Agreement before deducting estimated commissions and allocated fees of $0.6 million, 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.

During the nine months ended September 30, 2020, net cash provided by financing activities was $16.1 million, primarily consisting of cash proceeds from the SVB Term Loan of $14.0 million and gross cash proceeds of $2.5 million from sales of our common stock under the ATM Sales Agreement, before deducting estimated commissions and fees of $0.2 million.

***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 our ongoing Phase 2b/3 PRISM trial, the additional Phase 3 clinical trial we believe we will need to conduct to support the submission of an NDA to the FDA and a MAA to the EMA for Haduvio for the treatment of pruritus associated with prurigo nodularis, our ongoing Phase 2 CANAL trial, the costs of commercialization activities, including manufacturing capabilities, for Haduvio and other development activities including potentially commencing Phase 2 clinical trials for the treatment of

LID in patients with Parkinson's disease. In addition, we have incurred and may continue to incur additional expenses as a result of the COVID-19 pandemic and resulting clinical trial delays and interruptions. Furthermore, we expect to continue to incur additional 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. 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 for the treatment of pruritus associated with prurigo nodularis, as well as the scope, progress, timing, costs and results of clinical trials of Haduvio for other serious neurologically mediated conditions, including our ongoing Phase 2b/3 PRISM trial and our ongoing Phase 2 CANAL trial, as well as any future product candidates;
- the number and characteristics of indications for which we seek to develop Haduvio or any future product candidates and their respective development requirements;
- the outcome, timing and costs of clinical and nonclinical trials and of seeking regulatory approvals, including the costs of supportive clinical studies such as our planned human abuse liability, or 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 clinical development in connection with regulatory submissions;
- the costs of commercialization activities for Haduvio for the treatment of pruritus associated with prurigo nodularis or for any other serious neurologically mediated conditions 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 pruritus associated with prurigo nodularis or for any other serious neurologically mediated conditions or from any future product candidates;
- our ability to identify potential collaborators for Haduvio for the treatment of pruritus associated with prurigo nodularis 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 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;
- the costs of operating as a public company;
- our ability to continue as a going concern; and
- the impact of the COVID-19 pandemic on the scope, progress, timing, costs and results of our ongoing and planned clinical trials of Haduvio.

We believe that our existing cash and cash equivalents, including the proceeds from our October 2021 Private Placements, will enable us to fund our operating expenses and capital expenditure requirements into the fourth quarter of 2022, without giving effect to the rights of SVB under the SVB Loan Agreement if we fail to achieve either of the Milestone Conditions or fail to maintain at least $20.0 million in unrestricted and unencumbered cash in our accounts with SVB at any time prior to the satisfaction of the Milestone Conditions. If we fail to achieve any of the Milestone Conditions or to maintain the minimum cash requirement and SVB cash collateralizes the amounts then owed to SVB under the SVB Loan Agreement or uses such amounts to prepay the SVB Term Loan, the period for which we will be able to fund our operating expenses and capital expenditure requirements will be significantly shorter.

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 pruritus associated with 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 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.

**Critical Accounting Policies and Use of Estimates**

Our Condensed Consolidated Financial Statements have been prepared in accordance with U.S. generally accepted accounting principles. The preparation of these Condensed 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 Condensed 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.

We believe that the following critical accounting policies are most important to understanding and evaluating our reported financial results: research and development expense; stock-based compensation expense; income tax; and fair value measurements. Our critical accounting policies are described in the notes to the consolidated financial statements and under the heading "Management's Discussion and Analysis of Financial Condition and Results of Operations—Critical Accounting Policies and Use of Estimates" in our Annual Report on Form 10-K for the year ended December 31, 2020. During the nine months ended September 30, 2021, there were no material changes to our critical accounting policies.

**Off-Balance Sheet Arrangements**

Since our inception, we have not engaged in any off-balance sheet arrangements, as defined in the rules and regulations of the SEC. See Note 11 to our Condensed Consolidated Financial Statements included elsewhere in this Quarterly Report on Form 10-Q for discussion regarding our commitments and contingent commitments.

**Recently Adopted Accounting Pronouncements**

On January 1, 2021, we adopted Accounting Standards Update No. 2019-12-*Income Taxes (Topic 740)*, which simplifies the accounting for income taxes. The adoption of the new guidance did not affect our Condensed Consolidated Financial Statements.

**Recently Issued Accounting Pronouncements**

There have been no new accounting pronouncements during the nine months ended September 30, 2021 which could be expected to materially impact our Condensed Consolidated Financial Statements.

**Item 3. Quantitative and Qualitative Disclosures About Market Risk.**

Not Required.

**Item 4. 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, the Exchange Act, as of September 30, 2021. 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. Based on the evaluation of our disclosure controls and procedures as of September 30, 2021, our management, with the participation of 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.

**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 September 30, 2021 that has materially affected or is reasonably likely to materially affect, our internal control over financial reporting.

## PART II—OTHER INFORMATION

**Item 1. Legal Proceedings.**

We are not subject to any material legal proceedings.

**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 Quarterly Report on Form 10-Q 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 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, in our ongoing 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, although all sites are now allowing in-person monitoring visits. 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. In addition, the clinical sites in our ongoing Phase 2 trial for chronic cough in patients with IPF, which we refer to as the Phase 2 CANAL trial, suspended 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. While subject screening and enrollment for our Phase 2 CANAL trial resumed at certain clinical trial sites in the fourth quarter of 2020, all sites in the trial paused screening again in December 2020 in response to a shelter-in-place directive from the U.K. government. This shelter-in-place directive expired in March 2021 and the remaining COVID-19 pandemic related restrictions were lifted in July 2021. The U.K. government may choose to reinstate any and/or all of the restrictions in the future depending on COVID-19 infection rates. Screening activity has resumed and is steadily progressing at most sites following the lifting of the shelter-in-place directive. However, we expect that some sites may take longer to resume their trial activity as the clinical research related infrastructure was disrupted by the COVID-19 pandemic and that other sites may cease to participate in the trial entirely. The COVID-

19 pandemic 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 outbreak, restrictions on travel of patients and healthcare providers, potential unwillingness of subjects to enroll in trials at this time or the 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. In addition, we have taken temporary precautionary measures intended to help minimize the risk of the virus to our employees, including allowing employees to work remotely part of the week and suspending non-essential travel worldwide for our employees, each of which could negatively affect our business.

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. 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.

**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 $25.4 million and $32.8 million for the nine months ended September 30, 2021 and for the year ended December 31, 2020, respectively. As of September 30, 2021, we had an accumulated deficit of $172.4 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 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 to the ATM Sales Agreement, the SVB Term Loan and proceeds from the October 2021 Private Placements. We have devoted substantially all of 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 our ongoing Phase 2b/3 PRISM trial and our ongoing Phase 2 CANAL trial;
- complete other development work required for the filing of a NDA with the FDA and the filing of a MAA with the EMA for Haduvio for the treatment of pruritus associated with prurigo nodularis, including completing our Phase 2b/3 PRISM trial and at least one additional Phase 3 clinical trial in this indication;
- seek regulatory and marketing approvals for Haduvio for the treatment of pruritus associated with prurigo nodularis or for other serious neurologically mediated conditions or for any future product candidate that successfully 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 product 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.

In addition, we may incur additional expenses as a result of the COVID-19 pandemic and resulting clinical trial delays and interruptions. 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 pruritus associated with prurigo nodularis, we will be required, at a minimum, to successfully complete our ongoing Phase 2b/3 PRISM trial as well as an additional Phase 3 clinical trial 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 have identified conditions and events that raise substantial doubt about our ability to continue as a going concern.***

We believe there is substantial doubt about our ability to continue as a going concern as of the date of this Quarterly Report on Form 10-Q without additional capital. See Note 1 to the Condensed Consolidated Financial Statements appearing elsewhere in this Quarterly Report on Form 10-Q for additional information on our assessment. We plan to address this condition through the sale of common stock in public offerings and/or private placements, debt financings or other capital sources, including collaborations with other companies or other strategic transactions. If we are unable to obtain such funding and continue as a going concern, we might have to liquidate our assets and the values we receive for our assets in liquidation or dissolution could be significantly lower than the values reflected in our Condensed Consolidated Financial Statements. Our lack of cash resources and our conclusion that we may be

unable to continue as a going concern may materially adversely affect our share price and our ability to raise new capital or to enter into critical contractual relationships with third parties.

***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 nine months ended September 30, 2021 and the year ended December 31, 2020, we used net cash of $22.7 million and $29.0 million, respectively, in our operating activities, substantially all of which related to development activities for Haduvio. As of September 30, 2021, our cash and cash equivalents were $29.3 million and in October 2021 we received approximately $14.8 million in gross proceeds from our October 2021 Private Placements. We expect our expenses to increase substantially in connection with our ongoing activities, particularly as we continue to develop and conduct clinical trials of Haduvio, including our ongoing Phase 2b/3 PRISM trial and the additional Phase 3 clinical trial we believe we will need to conduct for Haduvio for the treatment of pruritus associated with prurigo nodularis and our other ongoing clinical trials, acquire or in-license rights to other potential product candidates or technologies and seek regulatory and marketing approvals for Haduvio or any future product candidate that successfully completes clinical trials, if any. In addition, we may incur additional expenses as a result of the COVID-19 pandemic and resulting clinical trial delays and interruptions. 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 and cash equivalents to fund the development of Haduvio for the treatment of pruritus associated with prurigo nodularis, for the treatment of chronic cough in patients with IPF 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 and cash equivalents will not be sufficient to complete development of Haduvio for the treatment of pruritus associated with 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 and cash equivalents, including the proceeds from our October 2021 Private Placements, will enable us to fund our operating expenses and capital expenditure requirements into the fourth quarter of 2022, without giving effect to the rights of SVB under the SVB Loan Agreement if we fail to achieve either of the Milestone Conditions or fail to maintain at least $20.0 million in unrestricted and unencumbered cash in our accounts with SVB at any time prior to the satisfaction of the Milestone Conditions. If we fail to achieve any of the Milestone Conditions and SVB cash collateralizes the amounts then owed to SVB under the SVB Loan Agreement or uses such amounts to prepay the SVB Term Loan, the period for which we will be able to fund our operating expenses and capital expenditure requirements will be significantly shorter.

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. 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 for the treatment of pruritus associated with prurigo nodularis, as well as the scope, progress, timing, costs and results of clinical trials of Haduvio for other serious neurologically mediated conditions, including our ongoing Phase 2 CANAL trial, as well as any future product candidates;
- the impacts of the COVID-19 pandemic on the scope, progress, timing, costs and results of our ongoing and planned clinical trials of Haduvio;

- the number and characteristics of indications for which we seek to develop Haduvio or any future product candidates and their respective development requirements;
- the outcome, timing and costs of clinical and nonclinical trials and of seeking regulatory approvals, including the costs of supportive clinical studies such as our planned HAL study and a potential TQT study;
- the costs associated with the manufacture of necessary quantities of Haduvio or any future product candidate for clinical development in connection with regulatory submissions;
- the costs of commercialization activities for Haduvio for the treatment of pruritus associated with prurigo nodularis or for any other serious neurologically mediated conditions 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 pruritus associated with prurigo nodularis or for any other serious neurologically mediated conditions or from any future product candidates;
- our ability to identify potential collaborators for Haduvio for the treatment of pruritus associated with prurigo nodularis 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 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;
- the costs of operating as a public company; and
- our ability to continue as a going concern.

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

On August 13, 2020, we entered into the SVB Loan Agreement with SVB, pursuant to which SVB provided the SVB Term Loan to us. In July 2021, we entered into the Loan Amendment. The SVB Term Loan bears 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 receives evidence satisfactory to it that we have (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 will be adjusted to a floating rate equal to the greater of (A) the prime rate plus 3.00% and (B) 6.25%. On the first business day of each month, we are required to make monthly interest payments and commencing on March 1, 2022, we will be 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.

Additionally, under the Loan Amendment, if we fail to achieve the Milestone Conditions, we will be required to deposit unrestricted and unencumbered cash equal to 100% of the principal amount of the SVB Term Loan then outstanding in a cash collateral account with SVB, which can be used by SVB to prepay the SVB Term Loan at any time. In addition, if we fail to maintain at least $20.0 million in unrestricted and unencumbered cash in our accounts with SVB at any time prior to the satisfaction of all the Milestone Conditions, we will be required to cash collateralize all outstanding amounts owed to SVB under the SVB Loan Agreement. We were also required under the Loan Amendment to raise at least $15.0 million in net proceeds from the sale of equity securities

from June 1, 2021 through October 31, 2021, which requirement was met through a combination of equity issuances under our ATM Sales Agreement and the proceeds from our October 2021 Private Placements.

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

- requiring us to dedicate a substantial portion of our cash and cash equivalents to the payment of interest on and principal of, our debt or maintain a substantial portion of our cash and cash equivalents in cash collateral accounts controlled by our lenders to secure repayment of our debt (which may be used by our lenders to prepay the debt if certain requirements relating to raising equity are not met), which will reduce the amounts available to fund working capital, capital expenditures, product development efforts and other general corporate purposes;
- obligating us to negative covenants restricting our activities, including the negative covenants to which we are subject 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 and cash equivalents 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. In addition, as discussed above, a failure to satisfy any Milestone Condition or to maintain at least $20.0 million in unrestricted and unencumbered cash in our accounts with SVB at any time prior to satisfaction of all of the Milestone Conditions could result in us having to deposit unrestricted and unencumbered cash equal to 100% of the principal amount of the SVB Term Loan then outstanding in a cash collateral account with SVB, which can be used by SVB to prepay the SVB Term Loan at any time. 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 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 our ongoing Phase 2b/3 PRISM trial and our other ongoing clinical trials as well as the additional Phase 3 clinical trial we believe we will need to conduct for Haduvio for the treatment of pruritus associated with prurigo nodularis and develop Haduvio for the treatment of other serious neurologically mediated conditions. 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 and to satisfy the requirements under the SVB Loan Agreement, including the requirement to raise substantial additional capital by June 30, 2022. 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 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.

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 of Haduvio for multiple serious neurologically mediated conditions. 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 program is the development of Haduvio for the treatment of pruritus associated with prurigo nodularis, as our efforts to develop Haduvio for other serious neurologically mediated conditions are only at an early stage. As a result, if our efforts to develop and commercialize Haduvio for the treatment of pruritus associated with prurigo nodularis 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 pruritus associated with prurigo nodularis, as well as for other serious neurologically mediated conditions, will depend on several factors, including the following:

- successfully recruiting, enrolling and retaining subjects in and completing our Phase 2b/3 PRISM trial;
- initiating and successfully recruiting, enrolling and retaining subjects in and completing additional clinical and nonclinical trials, including the additional Phase 3 clinical trial we believe we will need to conduct for Haduvio for the treatment of pruritus associated with prurigo nodularis and other supportive clinical studies such as our planned HAL study, a potential physical dependence study and a potential TQT study;
- demonstrating safety, tolerability and efficacy profiles that are satisfactory to the FDA, EMA and other comparable 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 and maintaining a commercially viable manufacturing process that is compliant with current good manufacturing practices, or cGMPs;
- obtaining, maintaining and protecting our patents, trade secrets and regulatory exclusivity in the U.S. and other countries;
- establishing a focused, specialty sales organization in the U.S. and successfully launching commercial sales following any marketing approval;
- obtaining commercial acceptance of our products, if approved, by patients, the medical community and third-party payors 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 serious neurologically mediated conditions is unproven.***

We are currently focused on the development and commercialization of Haduvio to treat serious neurologically mediated conditions. 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 pruritus and other serious neurologically mediated conditions and that Haduvio has the potential to be safe and well-tolerated, nalbuphine has not been approved in any indications other than pain. Additionally, Haduvio has not been approved in any indication, including the treatment of pruritus associated with prurigo nodularis, the lead indication for which we are pursuing clinical development of Haduvio. No therapies have been approved in the U.S. or Europe for the treatment of moderate to severe pruritus and we can provide no assurance that either Haduvio or any other future product candidate that we may seek to develop for this indication or for any other serious neurologically mediated condition 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, 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 or abandon product development programs;
- the number of subjects required for clinical trials may be larger than we anticipate, such as with the increase of the target number of enrolled subjects for our Phase 2b/3 PRISM trial from 240 to 360 subjects as a result of the SSRE analysis;
- subject enrollment in these clinical trials may be slower than we anticipate, whether as a result of the COVID-19 pandemic or otherwise, or participants may discontinue their participation in these clinical trials at a higher rate than we anticipate, as we experienced in our Phase 2 clinical trial of Haduvio for the treatment of pruritus associated with prurigo nodularis;
- the cost of planned clinical trials may be greater than we anticipate, as we have experienced in our Phase 2b/3 PRISM trial as we added additional sites, increased the target number of enrolled subjects as a result of the SSRE analysis, enrollment has taken longer than expected and we have used and expect to continue to use additional incentive strategies to address site activation and enrollment;
- our clinical trials 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 conducting clinical trials on our behalf, may deviate from applicable trial protocols, fail to comply with regulatory requirements or fail to 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 conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- subjects 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 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 are 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 for 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 characteristics of 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 data from preclinical studies and clinical trials;

- the FDA or comparable foreign regulatory authorities may fail to approve or subsequently find fault with the manufacturing 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 materials 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;
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change or the 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 other comparable foreign regulatory application that we submit for a product candidate or may conclude after review of our data that our application is insufficient to obtain marketing approval of a product candidate.

In addition to the above, the continued spread of COVID-19 globally could 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 if an outbreak occurs in their geography. The COVID-19 pandemic could also result in further delays in our clinical trials due to prioritization of hospital and medical resources toward the outbreak, restrictions in travel, potential unwillingness of patients to enroll in trials at this time 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.

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 desired;
- obtain marketing approval with labeling that includes significant use or distribution restrictions or significant safety warnings, 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.

Our failure to successfully and timely complete clinical trials of Haduvio for the treatment of pruritus associated with prurigo nodularis or for any other serious neurologically mediated condition 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 pruritus associated with prurigo nodularis failed to meet its primary endpoint and the number of subjects 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 pruritus associated with 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 Haduvio does not achieve the primary endpoint in our Phase 2b/3 PRISM trial or the FDA does not otherwise believe that the results of the 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 pruritus associated with 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.***

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 have used PROs as primary endpoints. For example, the primary endpoint of our Phase 2 clinical trial of Haduvio for the treatment of pruritus associated with prurigo nodularis was the proportion of patients reporting at least a 30% reduction from baseline to week 10 in seven-day mean Worst Itching 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. The primary endpoint of our Phase 2b/3 PRISM trial is 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 WI-NRS. 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, PROs for the assessment of pruritus have historically been observed to have high placebo group response rates. We observed this in some of our clinical trials of Haduvio. For example, in our Phase 2 clinical trial of Haduvio for the treatment of pruritus associated with prurigo nodularis, we observed a mean reduction from baseline in WI-NRS score for the trial's modified intention-to-treat population of 1.75 points for placebo as compared to 2.14 points for Haduvio dosed twice-daily at 81 mg and 2.51 points for Haduvio dosed twice-daily at 162 mg. 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 for pruritus 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 in pruritus, 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 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 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;
- 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 investigation; and
- the impact of the COVID-19 pandemic.

In particular, the successful completion of our clinical development program for Haduvio for the treatment of pruritus associated with prurigo nodularis is dependent upon our ability to enroll a sufficient number of subjects with this severe condition. We have experienced delays and difficulties in the enrollment of subjects in our clinical trials, including our Phase 2b/3 PRISM trial and our Phase 2 CANAL trial, which have delayed the completion of our trials. We have taken actions to increase enrollment, including increasing the number of clinical sites, providing sites with additional trial management staff and closing underperforming sites. However, these actions may not be successful. In addition, as a result of the COVID-19 pandemic, clinical sites for our Phase 2b/3 PRISM trial temporarily halted new subject screening and most subject enrollment and the clinical sites in our ongoing Phase 2 CANAL trial temporarily suspended enrollment and treatment of subjects in the trial due to the vulnerability of IPF patients to COVID-19 and we amended the protocol for the trial to reduce the number of in-person subject visits and procedures. While subject screening and enrollment for our Phase 2 CANAL trial resumed at certain clinical trial sites in the fourth quarter of 2020, all sites in the trial paused screening again in December 2020 in response to a shelter-in-place directive from the U.K. government. This shelter-in-place directive expired in March 2021 and other COVID-19 pandemic related restrictions were lifted in July 2021. The U.K. government may choose to reinstate any and/or all of the restrictions in the future depending on COVID-19 infection rates. Screening activity has resumed and is steadily progressing at most sites following the lifting of the shelter-in-place directive. However, we expect that some sites may take longer to resume their trial activity as the clinical research related infrastructure was disrupted by the COVID-19 pandemic and that other sites may cease to participate in the trial entirely.

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 prurigo nodularis in the case of our Phase 2b/3 PRISM trial and patients with IPF in the case of our Phase 2 CANAL trial and patients are generally only able to enroll in a single trial at a time. In addition, although there are no drugs approved in the U.S. or Europe for the treatment of pruritus associated with prurigo nodularis, many patients use various treatments off-label, such as antihistamines or gabapentin 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.

In response to the COVID-19 pandemic, the FDA issued guidance on March 18, 2020, and updated it on July 2, 2020, January 27, 2021 and August 30, 2021, to address the conduct of clinical trials during the pandemic. The guidance sets out a number of considerations for sponsors of clinical trials impacted by the pandemic, including the requirement to include in a clinical study report (or as a separate document) contingency measures implemented to manage the study, and any disruption of the study, as a result of the COVID-19 pandemic; a list of all study participants affected by COVID-19 pandemic related study disruptions by a unique subject identifier and by investigational site, and a description of how the individual's participation was altered; and analyses and corresponding discussions that address the impact of implemented contingency measures (e.g., participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the study. In its most recent update to this guidance, the FDA addressed questions received during the past year from clinical practitioners who are adapting their operations in a pandemic environment. These questions focused on, among other things, when to suspend, continue or initiate a trial and how to submit changes to protocols for investigational new drug applications and handle remote site monitoring visits. There is no assurance that this guidance governing clinical studies during the pandemic will remain in effect or, even if it does, that it will help address the risks and challenges enumerated above.

Any inability to enroll a sufficient number of subjects 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 and are associated with respiratory depression and potential cardiac risk. 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. To support our planned submission of an NDA to the FDA for Haduvio, we may be required to conduct a clinical trial of Haduvio to assess cardiac risk and, due to the association of opioids with endocrine dysfunction, a clinical trial 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 to complete a trial or result in potential product liability claims.

In our Phase 2 clinical trial of Haduvio for the treatment of pruritus associated with prurigo nodularis, the most frequently reported adverse events associated with Haduvio were nausea, dizziness and headache. In the open label extension of the trial, nausea, dizziness and fatigue were reported. Across both the Phase 2 clinical trial of Haduvio for the treatment of pruritus associated with prurigo nodularis and the open label extension, a total of four subjects reported SAEs, but none of these events was attributed to Haduvio.

In our Phase 2b/3 trial of Haduvio in patients with uremic pruritus, the most frequently reported adverse events attributed to Haduvio were nausea, vomiting, somnolence and dizziness. In patients with uremic pruritus, SAEs were frequent but were primarily related to associated underlying diseases or to procedural complications related to hemodialysis.

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.

***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 plan to conduct a HAL study to further characterize the abuse potential of oral nalbuphine. If the results of the HAL 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 classified 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 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 clinical development despite demonstrating positive results in preclinical studies or successfully advancing through Phase 1 and Phase 2 clinical trials. 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.

At a meeting with the FDA following the completion of our Phase 2 clinical trial of Haduvio for the treatment of pruritus associated with prurigo nodularis, the FDA advised us that the findings of the Phase 2 clinical trial may not be reliable and recommended that we conduct an additional Phase 2 dose ranging trial to identify the optimal dose and obtain reliable estimates of treatment effect for the recommended primary efficacy endpoint so as to better design and power our planned Phase 3 clinical trials. In providing such advice, the FDA noted the small number of subjects in each arm of the Phase 2 clinical trial and the large differential discontinuation rate among the three treatment arms, as well as our plan to increase the fixed-dose treatment duration from eight weeks in the Phase 2 clinical trial to 12 weeks in our Phase 2b/3 PRISM trial.

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. For example, we have designed our Phase 2b/3 PRISM trial based on an assumed discontinuation rate that takes into account observed discontinuation rates in our Phase 2 clinical trial of Haduvio for the treatment of pruritus associated with prurigo nodularis. If enrolled subjects withdraw from our Phase 2b/3 PRISM trial at a rate that is higher than expected, as occurred in our Phase 2 clinical trial of Haduvio for the treatment of pruritus associated with prurigo nodularis or at rates that are inconsistent across clinical sites and treatment arms, we may not achieve the primary endpoint of the trial, the validity or statistical significance of the trial could

be impaired and regulatory authorities may not view the trial as supportive of an application for marketing approval. 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 pruritus is drawn from *post hoc* analyses of data subsets from our Phase 2 clinical trials of Haduvio in patients with prurigo nodularis and uremic pruritus. While we believe these data may be useful in informing the design of our Phase 2b/3 PRISM trial and other 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 contraindication;
- 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-party 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 the treatment of pruritus associated with prurigo nodularis as our lead program. However, the development of Haduvio for this indication 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 in any of our target indications, we believe we will have the opportunity to commercialize it in the U.S. directly through our own focused, specialty sales organization. If Haduvio receives marketing approval outside the U.S., we may develop a variety of collaboration, distribution and other marketing arrangements with one or more third parties to commercialize the product in those markets.

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 pruritus associated with prurigo nodularis, we expect that it would compete with a number of therapeutics that are used off-label to treat prurigo nodularis, including anti-itch creams and emollients, oral or injectable antihistamines, Dupixent (dupilumab), which is an injectable prescription medicine approved for atopic dermatitis that is in clinical development for the treatment of pruritus associated with prurigo nodularis, 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; KPL-716, a monoclonal antibody targeting oncostatin M receptor beta being developed by Kiniksa Pharmaceuticals; CDX-0159, a humanized monoclonal antibody targeting the KIT receptor being developed by Celldex Therapeutics; and abrocitinib, an oral small molecule targeting the janus kinase 1 receptor being developed by Pfizer Inc. 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 pruritus associated with prurigo nodularis, could face competition from these product candidates, including difelikefalin, an oral kappa opioid receptor agonist being developed by Cara Therapeutics that is in Phase 2 clinical trials for chronic pruritus in patients with atopic dermatitis, chronic liver disease, chronic kidney disease and notalgia paresthetica.

If Haduvio is approved for the treatment of chronic cough associated with IPF, we expect that it would compete with product candidates currently in clinical development for the treatment of chronic cough associated with IPF, such as orvepitant, which is being developed by Nerre Therapeutics, and expect that it might also compete with other product candidates currently in development or submitted for approval to the FDA for the treatment of chronic refractory cough and unexplained chronic cough by companies including Merck, Shionogi, Bellus Health, Bayer, and Algernon Pharmaceuticals. 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 with IPF.

If Haduvio is approved for the treatment of LID in patients with Parkinson's disease, we expect that it would compete with Gocovri and Osmolex, which are extended-release capsule formulations of amantadine marketed by Adamas Pharmaceuticals, which is being acquired by Supernus Pharmaceuticals, and expect that it might also compete with other product candidates currently in development for the treatment of LID by companies including Addex Therapeutics and IRLAB Therapeutics. In addition, it is possible that product candidates currently in development for the treatment of Parkinson's disease by companies could, if approved, reduce the need for therapies to treat LID.

Many of our potential competitors, 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 and biotechnology 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.

***If the FDA or comparable foreign regulatory authorities approve generic versions of any of our products that receive marketing approval or such authorities do not grant our products appropriate periods of data exclusivity before approving generic versions of our products, the sales of our products could be adversely affected.***

Once an NDA is approved, the product covered thereby becomes a "reference-listed drug" in the FDA's publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," or the Orange Book. Manufacturers may seek approval of generic versions of reference-listed drugs through submission of abbreviated new drug applications, or ANDAs, in the U.S. In support of an ANDA, a generic manufacturer need not conduct clinical trials. Rather, the applicant generally must show that its product has the same active ingredient(s), dosage form, strength, route of administration and conditions of use or labeling as the reference-listed drug and that the generic version is bioequivalent to the 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 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 drug may be 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 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, or NCE. Specifically, in cases where such 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 that a patent covering the reference-listed drug is either invalid or will not be infringed by the generic product, in which case the applicant may submit its application four years following approval of the reference-listed drug. It is unclear whether the FDA will treat the active moieties in our product candidates as NCEs and, therefore, afford them five years of NCE data exclusivity if they are approved. If any product we develop does not receive five years of NCE exclusivity, the FDA may approve generic versions of such product three years after its date of approval, subject to the requirement that the ANDA applicant certifies to any patents listed for our products in the Orange Book. Manufacturers may seek to launch these generic products following the expiration of the applicable marketing exclusivity period, even if we still have patent protection for our product.

Competition from generic versions of any products we develop could negatively impact our future revenue, profitability and cash flows and substantially limit our ability to obtain a return on our investments in those products.

***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 $5.0 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 and expect to continue to rely, on third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials 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 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 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 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 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 clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, 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 government measures taken in response to the pandemic 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 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 prioritize the supply of other companies' products over Haduvio or any future product candidates or otherwise fail to satisfactorily perform according to the terms of the agreements between us and them or if unforeseen events in the manufacturing process arise;
- the possible termination or nonrenewal of agreements by our third-party contractors at a time that is costly or inconvenient 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 drug or 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 drug 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 government measures taken in response to the pandemic, 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. It is currently uncertain what impact, if any, Mallinckrodt's bankruptcy filing 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 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 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. In addition, if we are able to obtain marketing approval for any product candidates from foreign regulatory authorities, we intend to enter into strategic relationships with international biotechnology or pharmaceutical companies for the commercialization of those product candidates outside of 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 Quarterly Report on Form 10-Q 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 collaborations;
- collaborators may not perform their obligations as expected;
- collaborators may not pursue development and commercialization of the product candidates under the collaboration or may elect not to continue or renew development or commercialization programs, based on clinical trial results, changes in the collaborators' strategic focus or available funding or external factors, such as an acquisition of the collaborator, that divert resources or create competing priorities;
- collaborators may be involved in a business combination and could decide to delay, diminish or terminate the development 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 abandon 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 the 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 preferred course of development, might cause delays or termination of the research, development or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates or might result in litigation or arbitration, any of which would be time-consuming and expensive;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in 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 standards 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 are also party to an exclusive license agreement with Rutgers, the State University of New Jersey, under which we have licensed certain patent rights and know-how to develop and commercialize products incorporating nalbuphine for any human or animal use. 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. 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 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.

***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.

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 pruritus associated with prurigo nodularis or any other development program satisfies the requirements under Section 505(b)(2) of the FDCA or Section 505(b)(2) 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 commenced our Phase 2b/3 PRISM trial of Haduvio for the treatment of pruritus associated with prurigo nodularis and we believe we will need to conduct an additional Phase 3 clinical trial of Haduvio for the treatment of pruritus associated with prurigo nodularis 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 applicant and for which the applicant has not received a right of reference, which could expedite the development program for Haduvio for the treatment of pruritus associated with prurigo nodularis and any future product candidates 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 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 pruritus associated with prurigo nodularis 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.

Finally, disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including for 35 days beginning on December 22, 2018, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA, 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.

In response to the COVID-19 pandemic, on March 10, 2020, the FDA announced its intention to postpone most inspections of foreign manufacturing facilities and on March 18, 2020, the FDA temporarily postponed routine surveillance inspections of domestic manufacturing facilities. Subsequently, on July 10, 2020, the FDA announced its intention to resume certain on-site inspections of domestic manufacturing facilities subject to a risk-based prioritization system. The FDA intends to use this risk-based assessment system to identify the categories of regulatory activity that can occur within a given geographic area, ranging from mission critical inspections to resumption of all regulatory activities. In May 2021, the FDA issued a report in which it outlined its priorities for inspections moving forward given the ongoing uncertainties stemming from the pandemic. The agency indicated that inspections considered critical to the FDA's mission will remain the primary focus. When planning routine surveillance inspections, the agency will prioritize higher-risk establishments. Therefore, a longer interval between inspections will occur for the less high-risk facilities as the FDA adjusts to the impact of the COVID-19 pandemic. This means that postponed inspections will be prioritized based on risk and conducted over a longer period of time, ultimately increasing the amount of time between inspections of certain lower-risk facilities.

Regulatory authorities outside the United States may also impose similar restrictions or other policy measures in response to the COVID-19 pandemic. If a prolonged government shutdown occurs, or if global health concerns continue to prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews, or other regulatory activities, it could significantly impact the ability of the FDA or other regulatory authorities to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

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. 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 European Union, or 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, we could face heightened risks with respect to seeking marketing approval in the U.K. as a result of the recent withdrawal of the U.K. from the E.U., commonly referred to as Brexit. The U.K. and E.U. entered into a Trade and Cooperation Agreement in connection with Brexit that sets out certain procedures for approval and recognition of medical products in each jurisdiction. Since the regulatory framework for pharmaceutical products in the U.K. covering the quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from E.U. directives and regulations, Brexit could materially impact the future regulatory regime that applies to products and the approval of product candidates in the U.K. Any delay in obtaining or an inability to obtain, any marketing approvals, as a result of the Trade and Cooperation Agreement would prevent us from commercializing any product candidates in the U.K. and/or the E.U. and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the U.K. and/or E.U. for any product candidates or incur additional costs, which could significantly and materially harm our business.

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 Haduvio for the proposed indication of reduction of moderate to severe pruritus 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.

***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 and other 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 pruritus associated with prurigo nodularis. If we obtain regulatory approval to market Haduvio with an indication statement for the treatment of pruritus associated with 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 and other government agencies. While we have and may in the future conduct, clinical trials to evaluate the use of Haduvio to treat pruritic conditions other than pruritus associated with prurigo nodularis, Haduvio cannot be promoted for uses other than uses approved in the labeling by the FDA, EMA 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.

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, the FDA, the Federal Trade Commission 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.

***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 2030 under the Coronavirus Aid, Relief and Economic Security Act, or the CARES Act. 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.

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, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion 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 the constitutionality of the ACA. 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 U.S. To date, 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 drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for products. For example, on September 24, 2020, the Trump Administration finalized a rulemaking allowing states or certain other non-federal government entities to submit importation program proposals to the FDA for review and approval. Applicants are required to demonstrate that their importation plans pose no additional risk to public health and safety and will result in significant cost savings for consumers. The FDA has issued draft guidance that would allow manufacturers to import their own FDA-approved drugs that are authorized for sale in other countries (multi-market approved products).

In addition, President Trump issued several executive orders intended to lower the costs of prescription drug products. Certain of these orders are reflected in recently promulgated regulations, including an interim final rule implementing President Trump's most favored nation model, but such final rule is subject to a nationwide preliminary injunction for its failure to comply with notice and comment rulemaking requirements. The Biden Administration has frozen certain of the previous administration's measures to reform drug prices, pending further review. It remains to be seen how the Biden Administration will address this issue but, under Medicare Part D, the new administration may seek to establish a ceiling for the launch prices of all branded, biologic and certain generic drugs by referencing the average price of these drugs in other developed countries. At the same time, the administration may seek to limit Medicare Part D and public option drug prices through a tax penalty on manufacturers for increases in the cost of drugs and biologics above the general inflation rate. The Biden administration has agreed to delay for a year the implementation of one of President Trump's signature drug pricing policies, from January 2022 to 2023. The policy at issue would have prevented drug makers and middlemen from negotiating rebates on prescription drugs.

More recently, 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. Further, on August 21, 2021, the Centers for Medicare & Medicaid Services, or CMS, issued a proposed rule to rescind the Trump Administration's interim final rule, following public notice and comment. With issuance of this proposal, CMS stated that it will carefully consider the comments it received on the November 2020 interim final rule as it explores all options to incorporate value into payments for Medicare Part B drugs and improve beneficiaries' access to evidence-based care.

At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional health care 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.

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 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, 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.

***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.

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 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 California Consumer Privacy Act, or the CCPA, which went into effect on January 1, 2020, is creating similar risks and obligations as those created 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). Many other states are considering similar legislation. A broad range of legislative measures also have been introduced at the federal level. Accordingly, 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 the company 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 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 computer viruses, unauthorized access, 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. 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 and the development of Haduvio or any future product candidate could be significantly delayed.

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 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. 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.

**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 Medical Officer; and William Forbes, Pharm. D., our Chief Development 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 expand our organization and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.***

As of September 30, 2021, we had 26 employees. We expect to 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. Our expected 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 expected 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 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.

***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 or 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, including with respect to the substantial additional capital that we will need to raise by June 30, 2022 to satisfy the Milestone Conditions;
- 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;
- our obligations in connection with the SVB Term Loan;
- 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 has negatively affected 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 our company 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.

As of November 10, 2021, we have outstanding 25,846,577 shares of common stock, of which 790,562 shares are subject to restrictions on transfer under lock-up agreements entered into by our directors and officers in connection with the initial October 2021 private placement. These restrictions are due to expire on January 3, 2022. With the exception of the shares of common stock subject to such lock-up agreements, 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 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 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. In June 2020, we entered into the ATM Sales Agreement, pursuant to which, from time to time, we may offer and sell under the ATM Sales Agreement up to $12.0 million of the common stock registered under the Shelf Registration Statement pursuant to one or more "at-the-market" offerings. As of September 30, 2021, we had sold 3,583,394 shares of common stock for an aggregate purchase price of $10.9 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 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 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 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 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 Beneficial Ownership Limitations.

Similarly, on October 18, 2021, we issued to 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. If and when the Second Private Placement Form S-3 is declared effective, 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.

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 ATM Sales Agreement or otherwise, by Lincoln Park pursuant to the Form S-1, by the private placement investors pursuant to the Initial Private Placement Form S-3 or the Second 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, 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. Of the common stock warrants issued to the Initial Private Placement Investor, 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. As discussed above, the pre-funded warrants and the common stock warrants issued to the Initial Private Placement Investor are subject to Beneficial Ownership Limitations. As of November 10, 2021, all of the warrants issued to the Initial Private Placement Investor and NEA in the private placements remained outstanding. Although the Initial Private Placement Investor's warrants are subject to the 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, they 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 and/or NEA 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 Initial Private Placement Investor and NEA 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 and our significant stockholders, who have significant influence over our business, which may prevent new investors from influencing significant corporate decisions.***

Our executive officers and directors and their affiliates and our significant stockholders in the aggregate, beneficially own shares representing approximately 69.3% of our common stock as of November 10, 2021. As a result, our executive officers and directors and their affiliates and our significant stockholders acting together would be able to control 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, because many of these stockholders purchased their shares at prices substantially below our IPO price and have held their shares for a longer period, they may be more interested in selling our company to an acquirer than other investors or they may want us to pursue strategies that deviate from the interests of other stockholders.

***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. 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, 2020, we had federal and state net operating loss carryforwards of $137.6 million and federal research and development tax credit carryforwards of $3.9 million, which if not utilized generally will begin to expire in 2031 and 2032, respectively. These net operating loss and tax credit carryforwards could expire unused and be unavailable to offset future income tax liabilities. In general, under Section 382 of the 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 and research and development tax credit carryforwards to offset future taxable income. Due to our Series A convertible preferred stock financing in December 2012 and the shares issued in connection with our IPO in May 2019, an "ownership change" under Section 382 of the IRC occurred. As a result, our ability to use approximately $91.3 million of our net operating loss carryforwards and approximately $3.0 million of our research and development tax credits is limited. We may experience further ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. If a further ownership change occurs, our ability to use our net operating loss carryforwards might be further limited. We have not conducted a detailed study to document whether our historical activities qualify to support our research and development credit carryforwards. A detailed study could result in adjustment to our research and development credit carryforwards. If we determine that an ownership change occurs and our ability to use our historical net operating loss and tax credit carryforwards is materially limited or if our research and development tax credit carryforwards are adjusted, it would harm our future operating results by effectively increasing our future tax obligations.

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, 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), 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 losses arising in taxable years ending after December 31, 2017 (though any such NOLs may be carried forward indefinitely), the imposition of a one-time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, the elimination of U.S. tax on 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.

As part of Congress’s response to the COVID-19 pandemic, the Families First Coronavirus Response Act, or FFCR Act, was enacted on March 18, 2020 and the CARES Act was enacted on March 27, 2020. Both contain numerous tax provisions. In particular, the CARES Act retroactively and temporarily (for taxable years beginning before January 1, 2021) suspends application of the 80%-of-income limitation on the use of net operating losses, which was enacted as part of the Tax Act. It also provides 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.

Regulatory guidance under the Tax Act, the FFCR Act and the CARES Act 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 our company. 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.

***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 by-laws 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 that 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 acquisitions that have not been approved by our board of directors; and

- require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our certificate of incorporation or by-laws.

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 by-laws 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.

**Item 2. Unregistered Sales of Equity Securities and Use of Proceeds.**

**Unregistered Sales of Equity Securities**

Except as previously disclosed on a Current Report on Form 8-K (File No. 001-38886) that we filed with the SEC on June 21, 2021, we did not sell or issue any equity securities during the three months ended September 30, 2021 that were not registered under the Securities Act.

**Use of Proceeds from IPO of Common Stock**

On May 9, 2019, we closed our IPO, in which we issued and sold 5,500,000 shares of common stock at a public offering price of $10.00 per share. The aggregate gross proceeds to us from our IPO were $55.0 million.

All of the shares of common stock issued and sold in our IPO were registered under the Securities Act pursuant to a registration statement on Form S-1 (Registration No. 333-230745), which was declared effective by the SEC on May 7, 2019. The aggregate net proceeds to us from the IPO were approximately $48.2 million, after deducting underwriting discounts and commissions and offering expenses payable by us of approximately $6.8 million.

No offering expenses were paid directly or indirectly to any of our directors or officers (or their associates) or persons owning 10% or more of any class of our equity securities or to any other affiliates.

As of September 30, 2021, we used approximately $43.5 million of the net proceeds from the IPO to fund the development of Haduvio for the treatment of pruritus associated with prurigo nodularis, the treatment of chronic cough in patients with IPF and general corporate purposes. There has been no material change in our planned use of the net proceeds from the IPO as described in our final prospectus for the IPO filed with the SEC pursuant to Rule 424(b) under the Securities Act. We have invested the net proceeds from the IPO in money market funds.

**Item 6. Exhibits.**

| Exhibit Number | Description |
|---|---|
| 4.1 | 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) |
| 4.2 | 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) |
| 4.3 | 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) |
| 4.4 | 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) |
| 4.5 | 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) |
| 10.1 | 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) |
| 10.2* | Second Amendment to Loan and Security Agreement, dated August 13, 2021, by and between Silicon Valley Bank and the Registrant |
| 10.3 | 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) |
| 10.4 | 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) |
| 10.5 | 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) |
| 10.6 | 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) |
| 31.1* | Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) or 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002 |
| 31.2* | Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) or 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002 |
| 32.1* | Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 |
| 32.2* | Certification of Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 |
| 101.INS* | Inline XBRL Instance Document – the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document. |
| 101.SCH* | Inline XBRL Taxonomy Extension Schema Document |
| 101.CAL* | Inline XBRL Taxonomy Extension Calculation Linkbase Document |
| 101.DEF* | Inline XBRL Taxonomy Extension Definition Linkbase Document |
| 101.LAB* | Inline XBRL Taxonomy Extension Label Linkbase Document |
| 101.PRE* | Inline XBRL Taxonomy Extension Presentation Linkbase Document |
| 104 | Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101). |

* Filed herewith.

**SIGNATURES**

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

TREVI THERAPEUTICS, INC.

Date: November 10, 2021

By: /s/ Jennifer L. Good

**Jennifer L. Good**
**President and Chief Executive Officer**
**(Principal Executive Officer)**

By: /s/ Lisa Delfini

**Lisa Delfini**
**Chief Financial Officer**
**(Principal Financial Officer)**

**SECOND AMENDMENT**
**TO**
**LOAN AND SECURITY AGREEMENT**

This Second Amendment to Loan and Security Agreement (this "Amendment") is entered into this 13th day of August 2021, by and between **SILICON VALLEY BANK** ("Bank") and **TREVI THERAPEUTICS, INC.**, a Delaware corporation ("Borrower") whose address is 195 Church Street, 14th Floor, New Haven, Connecticut 06510.

**RECITALS**

**A.** Bank and Borrower have entered into that certain Loan and Security Agreement dated as of August 13, 2020, as amended by that certain First Amendment to Loan and Security Agreement dated as of July 6, 2021 between Borrower and Bank (the "**First Amendment**") (as the same may from time to time be further amended, modified, supplemented or restated, the "Loan Agreement").

**B.** Bank has extended credit to Borrower for the purposes permitted in the Loan Agreement.

**C.** Borrower has requested that Bank amend the Loan Agreement to make certain revisions to the Loan Agreement as more fully set forth herein.

**D.** Bank has agreed to so amend certain provisions of the Loan Agreement, but only to the extent, in accordance with the terms, subject to the conditions and in reliance upon the representations and warranties set forth below.

**AGREEMENT**

**NOW, THEREFORE,** in consideration of the foregoing recitals and other good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, and intending to be legally bound, the parties hereto agree as follows:

**1. Definitions.** Capitalized terms used but not defined in this Amendment shall have the meanings given to them in the Loan Agreement.

**2. Amendments to Loan Agreement.**

**2.1 Section 13.1** (**Definitions**). The following term and its respective definition set forth in Section 13.1 is amended in its entirety and replaced with the following:

" "**Designated Deposit Account**" is the account number ending 291 (last three digits) maintained by Borrower with Bank (provided, however, if no such account number is included, then the Designated Deposit Account shall be any deposit account of Borrower maintained with Bank as chosen by Bank)."

**3. Limitation of Amendments.**

**3.1** The amendments set forth in Section 2, above, are effective for the purposes set forth herein and shall be limited precisely as written and shall not be deemed to (a) be a consent to any amendment, waiver or modification of any other term or condition of any Loan Document, or (b) otherwise prejudice any right or remedy which Bank may now have or may have in the future under or in connection with any Loan Document.

**3.2** This Amendment shall be construed in connection with and as part of the Loan Documents and all terms, conditions, representations, warranties, covenants and agreements set forth in the Loan Documents, except as herein amended, are hereby ratified and confirmed and shall remain in full force and effect.

**4. Representations and Warranties.** To induce Bank to enter into this Amendment, Borrower hereby represents and warrants to Bank as follows:

**4.1** Immediately after giving effect to this Amendment (a) the representations and warranties contained in the Loan Documents are true and correct in all material respects as of the date hereof (except to the extent such representations and warranties relate to an earlier date, in which case they are true and correct in all material respects as of such date), and (b) no Event of Default has occurred and is continuing;

**4.2** Borrower has the power and authority to execute and deliver this Amendment and to perform its obligations under the Loan Agreement, as amended by this Amendment;

**4.3** The organizational documents of Borrower delivered to Bank on the Effective Date, remain true, accurate and complete and have not been amended, supplemented or restated and are and continue to be in full force and effect;

**4.4** The execution and delivery by Borrower of this Amendment and the performance by Borrower of its obligations under the Loan Agreement, as amended by this Amendment, have been duly authorized;

**4.5** The execution and delivery by Borrower of this Amendment and the performance by Borrower of its obligations under the Loan Agreement, as amended by this Amendment, do not contravene (a) any material Requirement of Law, (b) any material agreement binding on Borrower, (c) any order, judgment or decree of any court or other governmental or public body or authority, or subdivision thereof, binding on Borrower, or (d) the organizational documents of Borrower;

**4.6** The execution and delivery by Borrower of this Amendment and the performance by Borrower of its obligations under the Loan Agreement, as amended by this Amendment, do not require any action by, filing (other than a financing statement), registration, or qualification with, or Governmental Approval from, any Governmental Authority (except such Governmental Approvals which have already been obtained or made); and

**4.7** This Amendment has been duly executed and delivered by Borrower and is the binding obligation of Borrower, enforceable against Borrower in accordance with its terms, except as such enforceability may be limited by bankruptcy, insolvency, reorganization, liquidation, moratorium or other similar laws of general application and equitable principles relating to or affecting creditors' rights.

**5. Ratification of Perfection Certificate**. Borrower hereby ratifies, confirms and reaffirms, all and singular, the terms and disclosures contained in a certain Perfection Certificate dated as of August 13, 2020, as amended by Schedule 2 of the First Amendment, and acknowledges, confirms and agrees that the disclosures and information Borrower provided to Bank in such Perfection Certificate, as amended by Schedule 2 of the First Amendment, have not changed, as of the date hereof.

**6. Integration**. This Amendment and the Loan Documents represent the entire agreement about this subject matter and supersede prior negotiations or agreements. All prior agreements, understandings, representations, warranties, and negotiations between the parties about the subject matter

of this Amendment and the Loan Documents merge into this Amendment and the Loan Documents.

**7. Counterparts.** This Amendment may be executed in any number of counterparts and all of such counterparts taken together shall be deemed to constitute one and the same instrument.

**8. Effectiveness**. This Amendment shall be deemed effective upon (a) the due execution and delivery to Bank of this Amendment by each party hereto and (b) Borrower's payment to Bank of Bank's reasonable and documented legal fees and expenses incurred in connection with this Amendment which shall have been invoiced within five (5) days of the date hereof.

*[Signature page follows.]*

**In Witness Whereof,** the parties hereto have caused this Amendment to be duly executed as a sealed instrument under the laws of the Commonwealth of Massachusetts and delivered as of the date first written above.

| **BANK** | **BORROWER** |
| --- | --- |
| SILICON VALLEY BANK | TREVI THERAPEUTICS, INC. |
| By: /s/ Lauren Cole | By: /s/ Jennifer Good |
| Name: Lauren Cole | Name: Jennifer Good |
| Title: Director | Title: President and Chief Executive Officer |

**Exhibit 31.1**

**CERTIFICATION PURSUANT TO RULES 13a-14(a) OR 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 Quarterly Report on Form 10-Q 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(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

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

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

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

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

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

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

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

Date: November 10, 2021

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) OR 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 Quarterly Report on Form 10-Q 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(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

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

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

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

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

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

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

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

Date: November 10, 2021

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 Quarterly Report on Form 10-Q of Trevi Therapeutics, Inc. (the "Company") for the period ended September 30, 2021, 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: November 10, 2021

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 Quarterly Report on Form 10-Q of Trevi Therapeutics, Inc. (the "Company") for the period ended September 30, 2021, 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: November 10, 2021

By: /s/ Lisa Delfini
Lisa Delfini
Chief Financial Officer
(Principal Financial Officer)