UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 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 001-4078

ELIEM THERAPEUTICS, INC.

(Exact name of Registrant as specified in its Charter)

Delaware	**83-2273741**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
23515 NE Novelty Hill Road, Suite B221 #125 Redmond, WA	**98053**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (425) 276-2300

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

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, par value $0.0001 per share	**ELYM**	**The Nasdaq Stock Market LLC (The Nasdaq Global Market)**

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

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

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

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

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

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

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

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

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

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

The registrant's common stock was not publicly traded as of the last business day of the registrant's most recently completed second fiscal quarter.

As of February 28, 2022, the registrant had 26,567,681 shares of common stock, $0.0001 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2022 Annual Meeting of Stockholders, which the registrant intends to file pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year ended December 31, 2021, are incorporated by reference into Part III of this Annual Report on Form 10-K.

Table of Contents

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K and the information incorporated herein by reference contain forward-looking statements about us and our industry that involve substantial risks and uncertainties. All statements other than statements of historical facts contained in this Annual Report on Form 10-K, including statements regarding our future results of operations, financial condition, business strategy and plans and objectives of management for future operations, are forward-looking statements. In some cases, you can identify forward-looking statements because they contain words such as “anticipate,” “believe,” “contemplate,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “will,” or “would,” or the negative of these words or other similar terms or expressions. Forward-looking statements in this Annual Report on Form 10-K include, but are not limited to, statements about:

- the success, cost and timing of our product development activities and clinical trials;
- our ability to obtain and maintain regulatory approval of our product candidates;
- our ability to successfully commercialize any of our products that are approved;
- the rate and degree of market acceptance of our products;
- the size and growth potential of the markets for our product candidates, if approved for commercial use, and our ability to serve those markets;
- our estimates of our expenses, ongoing losses, future revenues, capital requirements and our needs for or ability to obtain additional financing;
- the sufficiency of our capital resources to fund operations for the time periods referenced;
- our ability to obtain and maintain intellectual property protection for our products and product candidates;
- the ability to scale up manufacturing of our product candidates to commercial scale;
- our ability to successfully establish and successfully maintain appropriate collaborations;
- our reliance on third parties to conduct our clinical trials;
- our reliance on third-party contract manufacturers to manufacture and supply our product candidates for us;
- our ability to identify and develop new products and product candidates;
- our ability to enroll patients in our clinical trials at the pace that we project;
- ability to retain and recruit key personnel;
- our ability to obtain funding for our operations, including funding necessary to develop and commercialize our product candidates;
- the potential effects of the COVID-19 pandemic on our clinical development and business;
- our financial performance; and
- developments and projections relating to our competitors or our industry.

You should refer to the section of this Annual Report on Form 10-K titled “Risk Factors” for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. New risk factors may emerge from time to time and it is not possible for our management to predict all risk factors, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements.

You should not rely on forward-looking statements as predictions of future events. We have based the forward-looking statements contained in this Annual Report on Form 10-K primarily on our current expectations and projections about future events and trends that we believe may affect our business, financial condition and operating results. We undertake no obligation to update any forward-looking statements made in this Annual Report on Form 10-K to reflect events or circumstances after the date of this Annual Report on Form 10-K or to reflect new information or the occurrence of unanticipated events, except as required by law. 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. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments.

In addition, statements that “we believe” and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based on information available to us as of the date of this Annual Report on Form 10-K. While we believe that information provides a reasonable basis for these statements, that information may be limited or incomplete. Our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all relevant information. These statements are inherently uncertain, and investors are cautioned not to unduly rely on these statements.

You should read this Annual Report on Form 10-K with the understanding that our actual future results, levels of activity, performance and achievements may be different from what we expect. We qualify all of our forward-looking statements by these cautionary statements.

Risk Factor Summary

Our business is subject to numerous risks and uncertainties. This summary does not address all of the risks that we face. Additional discussion of the risks summarized in this risk factor summary, and other risks that we face, can be found below under the heading "Risk Factors" under Part I, Item 1A of this Annual Report. These risks include, but are not limited to, the following:

- We have incurred significant losses since our inception, anticipate that we will incur substantial losses for the foreseeable future, and may never achieve or maintain profitability. We had an accumulated deficit of $75.6 million and $28.1 million as of December 31, 2021 and December 31, 2020, respectively.
- We expect to rely on capital markets, and to a lesser extent, United Kingdom research and development tax credits and incentives, for additional funding to conduct our future clinical trials and to complete development and commercialization of our product candidates. If we are unable to access capital when needed, we would be forced to delay, reduce or eliminate our clinical development programs or commercialization efforts.
- We have never generated any revenue from product sales, and we may never generate revenue or be profitable.
- Our business substantially depends upon the successful development, regulatory approval and commercialization of ETX-810 and ETX-155.
- Clinical development involves a lengthy, complex and expensive process, with an uncertain outcome. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and the results of our clinical trials may not satisfy the requirements of the FDA or comparable foreign regulatory authorities.
- We have never commercialized a product candidate and we may lack the necessary expertise, personnel and resources to successfully commercialize any of our products that receive regulatory approval on our own or together with collaborators.
- We face significant competition from other pharmaceutical and biotechnology companies and other research organizations and our operating results will suffer if we fail to compete effectively.
- Public health crises such as pandemics or similar outbreaks could materially and adversely affect our preclinical and clinical trials, business, financial condition and results of operations.
- We rely, and expect to continue to rely, on third parties to conduct, supervise and monitor our preclinical studies and clinical trials, and those third parties may not perform satisfactorily, including by failing to meet deadlines for the completion of such trials or failing to comply with regulatory requirements.
- We rely, and expect to continue to rely, on third parties to manufacture our clinical and ultimately commercial product supply. Those third parties may not perform satisfactorily, including by failing to meet product specifications, required demand or cost-efficient scale levels.
- If we are unable to obtain, maintain and protect sufficient patent and other intellectual property rights for our product candidates and technology, or if the scope of patent and other intellectual property rights obtained is not sufficiently broad, we may not be able to compete effectively in our market.
- We have identified material weaknesses in our internal control over financial reporting. If we are unable to remediate these material weaknesses, or if we identify additional material weaknesses in the future or otherwise fail to maintain effective internal control over financial reporting, we may not be able to accurately or timely report our financial condition or results of operations, which may adversely affect our business.

PART I

Item 1. Business

Company Overview

We are a clinical-stage biotechnology company focused on developing novel therapies for neuronal excitability disorders to address unmet needs in chronic pain, psychiatry, epilepsy and other disorders of the peripheral and central nervous systems. These disorders often occur when neurons are overly excited or inhibited, leading to an imbalance, and our focus is on restoring homeostasis. We are developing a pipeline of clinically differentiated product candidates focused on validated mechanisms of action with broad therapeutic potential to deliver improved therapeutics for patients with these disorders.

Our two lead clinical-stage candidates are ETX-810 and ETX-155. ETX-810 is a novel palmitoylethanolamide (PEA) prodrug initially being developed for the treatment of diabetic peripheral neuropathic pain (DPNP) and lumbosacral radicular pain (LSRP, commonly referred to as sciatica). ETX-810 is being evaluated in two Phase 2a clinical trials that are expected to report topline data in 2022 (DPNP Phase 2a in the first half of 2022, and LSRP Phase 2a in the second half of 2022). ETX-155 is a neurosteroid $GABA_A$ receptor positive allosteric modulator (PAM) initially being developed for major depressive disorder (MDD), perimenopausal depression (PMD) and focal onset seizures (FOS), the most common type of seizure in people with epilepsy. In the first half of 2022, assuming U.S. Food and Drug Administration (FDA) clearance of our investigational new drug (IND) application filed in the first quarter of 2022, we plan to initiate two Phase 2a clinical trials for ETX-155 in patients with MDD and PMD, and we expect both to report topline data in the second half of 2023. In addition, we have initiated a Phase 1b proof-of-concept clinical trial in patients with photosensitive epilepsy that is expected to report interim data in the first half of 2022.

We focus on the development of product candidates whose mechanisms of action have been clinically validated. By clinically validated, we mean there are product candidates with these mechanisms of action that have demonstrated statistical significance on efficacy endpoints in published randomized, controlled clinical trials. We leverage the deep expertise of our team to generate new chemical entities (NCEs) based on these clinically validated mechanisms of action that we believe have the potential to be clinically differentiated and enhance patient outcomes. Through this approach, we have established a robust pipeline with two clinical product candidates and two preclinical programs, each with the potential to address multiple disorders. Our product candidates are focused on addressing neuronal excitability disorders with large, well-defined markets, where clinical and regulatory endpoints are clearly established and development pathways are precedented, yet current therapies leave patients with efficacy, safety or tolerability challenges. Our strategy is to initially pursue indications for each of our product candidates where the clinical translatability of the mechanism of action has been well established and, upon demonstrating clinical proof of concept, evaluate additional indications to maximize the value of each program. We believe these principles favorably position us to bring novel therapeutics to patients living with challenging disorders while maximizing our probability of clinical development, regulatory and commercial success.

Our lead investigational program, ETX-810, is a novel, oral, NCE prodrug of PEA in clinical development for chronic pain conditions. Despite a large global prescription drug market for chronic pain therapeutics, it has been shown that less than half of patients achieve a 50 percent reduction in their pain intensity with current first line therapies. In addition to suboptimal efficacy, current therapies are often hindered by dose-limiting side effects such as dizziness, sedation, cognitive impairments, gastrointestinal disturbances and concerns over abuse liability. Despite these issues, drugs to treat chronic pain, such as Lyrica and Cymbalta, have achieved significant commercial success and have been among the top-selling pharmaceutical products globally.

The PEA pathway, which is believed to play an important role in the regulation of neuroinflammation and pain signaling, represents a promising potential mechanism to treat multiple conditions of chronic pain. PEA is an endogenous bioactive lipid that has been evaluated in dietary supplement formulations in relation to various pain conditions in more than 30 clinical studies, with over 2,500 patients, including patients with LSRP and DPNP, treated with dietary supplement PEA in these studies. Fifteen of these studies were randomized, controlled trials (RCTs) in a total of approximately 1,500 patients, with thirteen RCTs demonstrating a statistically significant improvement in pain reduction endpoints. A peer-reviewed meta-analysis of eight RCTs conducted with PEA demonstrated a weighted mean reduction in pain intensity score (based on a Visual Analog Scale (VAS)) of approximately two points compared to control, which compares favorably to the reductions in pain intensity reported from clinical trials with currently approved chronic pain medications. In addition, few adverse events related to PEA treatment have been reported in these published clinical studies. Despite this promising precedent clinical data supporting the exploration of the potential utility of PEA in chronic pain treatment, there are no PEA-based therapeutics approved by the FDA, European Medicines Agency (EMA) or similar regulatory authority. Rather, PEA is only currently available as a dietary supplement (nutraceutical), which has shown low bioavailability and overall poor drug-like properties.

As a prodrug of PEA, ETX-810 was designed to significantly improve the absorption and systemic exposure of PEA beyond what is achievable with currently available formulations, potentially maximizing the therapeutic effect. In our Phase 1 SAD and MAD clinical trials of ETX-810, which included a total of 80 healthy volunteers, ETX-810 demonstrated encouraging safety and tolerability. ETX-810 also demonstrated improved pharmacokinetics in a group of healthy subjects relative to dietary supplement formulations of PEA, with approximately three times higher PEA exposure on a matched dose basis. We believe the optimized pharmacokinetics and favorable tolerability of ETX-810, combined with our development and manufacturing expertise, put us in position to progress a robust clinical development program and explore the full therapeutic effect of ETX-810. To date, we have not observed any clinically relevant drug-drug interactions with ETX-810, and due to PEA's endogenous nature, we believe there is a low potential for liabilities related to addiction or abuse, positioning ETX-810 to potentially be used as a differentiated monotherapy or in combination with other medications for chronic pain. If approved, ETX-810 may be the first PEA-based therapeutic addressing the critical unmet need in chronic pain treatment for novel, non-opioid and non-addictive therapeutic options. We believe a significant commercial opportunity exists for a new chronic pain agent with proven efficacy and a favorable safety and tolerability profile.

We have initiated two separate Phase 2a clinical trials of ETX-810 in the United States, one in patients with DPNP and another in patients with LSRP, to evaluate the efficacy and safety of ETX-810 in these indications. We expect to report topline data from our DPNP Phase 2a trial in the first half of 2022, and from the LSRP Phase 2a trial in the second half of 2022. If these trials are successful, we plan to conduct further studies with a view to broaden ETX-810's clinical applications in peripheral neuropathic and other chronic pain conditions.

Our second clinical program, ETX-155, is an investigational, oral, neuroactive steroid NCE that is designed to act as a positive allosteric modulator of the $GABA_A$ receptor ($GABA_AR$) and that we are planning to evaluate in patients with depression and epilepsy. MDD affects approximately 35 million adults globally and approximately 19 million adults in the United States and causes significant impairment to daily life. While there are effective therapies available for individuals suffering from MDD, there is considerable variability in patient responsiveness resulting in only about one-third of patients benefiting from their first line therapy. There is a pressing need for safe, well-tolerated and rapidly acting antidepressants that reliably provide clinical improvement faster than the up to six weeks associated with standard of care selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Epilepsy affects approximately 4.7 million people in the major markets of the United States, Europe, and Japan, with approximately 1 million of these patients experiencing uncontrolled focal onset seizures (FOS) that are refractory to multiple anti-seizure medications (ASMs). Despite the existence of over 30 approved ASMs, approximately 30% of epilepsy patients fail to achieve adequate seizure control. FOS has a high prevalence of psychiatric co-morbidities like depression, which can be exacerbated by many of the currently prescribed ASMs. There is a pressing need for new ASMs to not only reduce the number of seizures but to also provide a positive effect on mood. The $GABA_A$ PAM therapeutic class has been clinically validated in certain depression and epilepsy indications, and we believe there is a clear opportunity for clinical differentiation.

ETX-155 was designed to have dual potency at both synaptic and extrasynaptic $GABA_A$ receptors. ETX-155 has also shown differentiated pharmacokinetic properties, including no clinically meaningful food effect and an approximate 40-hour half-life to enable once-a-day dosing. Results from our 7-day and 14-day Phase 1 repeat dose clinical trials demonstrated favorable tolerability data at exposure levels that are consistent with dosing levels that achieved robust activity in preclinical models of depression, anxiety and epilepsy. Based on our preclinical and clinical work to date, we plan to pursue clinical trials in FOS, MDD and PMD. In the second half of 2021, we initiated a Phase 1b photosensitive epilepsy trial, which if successful, would support initiating a Phase 2 clinical trial in FOS. We plan to announce interim data from the photosensitive epilepsy trial in the first half of 2022. In addition, assuming FDA clearance of our IND filed in the first quarter of 2022 with the psychiatry division, we intend to initiate a Phase 2 clinical trial in patients with MDD in the first half of 2022 and expect to report topline data in the second half of 2023. We also intend to initiate a Phase 2 clinical trial to support clinical efficacy in patients with PMD in the first half of 2022, assuming FDA clearance of our IND, and expect to report topline data in the second half of 2023.

In addition to our clinical candidates, we are progressing a preclinical pipeline with two programs currently in discovery stage. Our preclinical programs apply our medicinal chemistry and biology expertise combined with our in-depth understanding of drug discovery and development processes to develop novel product candidates based on clinically validated mechanisms of action.

Our lead preclinical program is a Kv7.2/3 potassium channel opener. Kv7.2/3 has been clinically validated as a therapeutic target for both epilepsy and pain. The first generation Kv7 channel opener, ezogabine (Potiga), was approved for refractory focal onset seizures in 2011 in both the United States and in Europe (where it was known as retigabine, or Trobalt). Flupirtine (Katadolon) was another first generation Kv7.2/3 opener that provided clinical validation and was used in Europe as a treatment for pain. These molecules showed clinical efficacy but subsequently had to be withdrawn from the market due to safety issues. We are developing an NCE that harnesses the efficacy of the Kv7.2/3 channel mechanism while attempting to improve the safety and tolerability relative to earlier molecules, based on our insights into the mechanisms of toxicity. We expect to initiate IND-enabling studies for this program in 2022.

Our second preclinical program is focused on developing a novel, potent analog of an earlier approved 2,3-benzodiazepine for the potential treatment of generalized anxiety disorder (GAD). The aim of our program is to develop a rapidly acting, non-sedating, non-addictive anxiolytic that does not impair motor or cognitive performance, does not have any adverse drug-drug interactions, and has the potential to be dosed once a day. We plan to progress preclinical development activities for this program in 2022.

We own the rights to our product candidates through both acquisitions and internal research and development efforts. With respect to ETX-810, in February 2019 we acquired in-process research and development (IPR&D) related to the ETX-810 program from Carnot, LLC. With respect to ETX-155, in October 2020, we acquired 100% of the share capital of Athenen Therapeutics, Inc., which included IPR&D related to the ETX-155 program. Following these acquisitions, we have continued the in-house clinical-stage development of the ETX-155 and ETX-810 programs. Our preclinical Kv7 and GAD programs have been developed by us.

Below is a summary of our wholly owned pipeline.

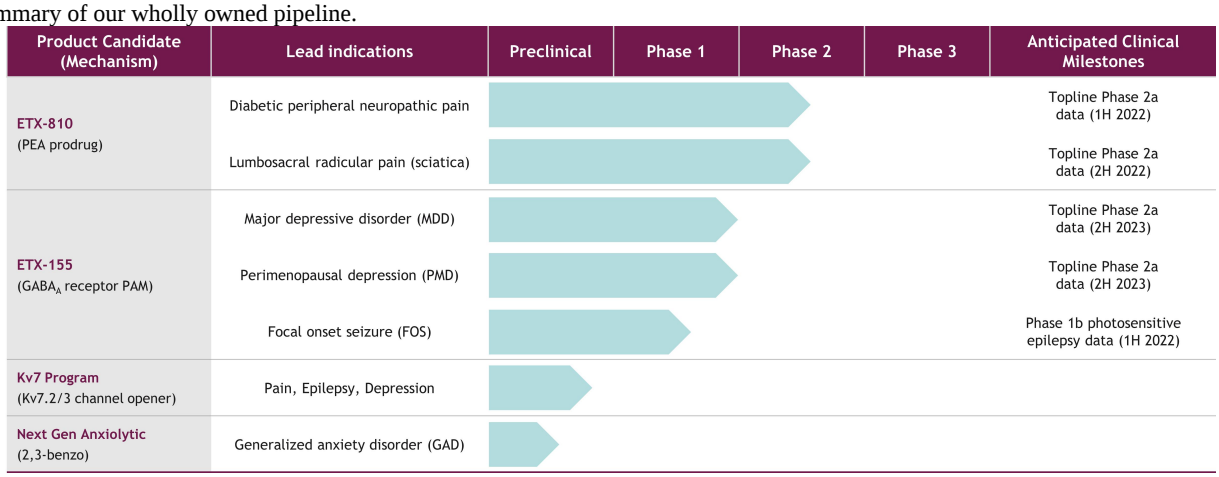

Figure 1. Eliem Therapeutics' pipeline of product candidates.

Our Approach

We follow several key principles to guide our research and development efforts that we believe will enable us to efficiently bring clinically differentiated therapies to market to help millions of people suffering from central nervous system (CNS) disorders:

- ***Focus on clinically validated mechanisms of action.*** We concentrate our research and development efforts on opportunities within the broad range of neuronal excitability disorders, where there has been prior clinical validation for the mechanism of action or pathway and where significant unmet need exists due to efficacy and safety limitations of existing therapies. By focusing on products with mechanisms of action that have clinical validation, we believe we can reduce the clinical translational risk of our product candidates while leveraging our extensive neuroscience drug development expertise to develop products that have the potential to meaningfully improve clinical outcomes.

- ***Establish clinical differentiation for our product candidates.*** We leverage the deep chemistry, neuroscience and manufacturing expertise of our team to generate NCEs which we believe can be clinically differentiated and enhance patient outcomes. We intend to improve on efficacy, safety and tolerability limitations of existing therapies that impact patient convenience, compliance and outcomes. We aim to deliver therapeutic candidates with optimal pharmacological properties that make them both clinically differentiated and commercially attractive.
- ***Pursue CNS indications with well-defined regulatory pathways in large markets that are inadequately served by current therapies.*** The initial indications we are pursuing for ETX-810 and ETX-155 are chronic pain, depression and epilepsy, all of which have well-characterized, large patient populations and are insufficiently addressed by existing therapies. In these indications, clinical endpoints and regulatory pathways are well-defined and precedented.
- ***Develop products that have broad therapeutic potential***. We believe that the biological pathways that are involved in many neuronal excitability disorders are related, and therefore, therapies that effectively address these pathways may be applicable in multiple CNS disorders. Our strategy for each product candidate is to initially pursue tractable indications where the clinical translatability of the mechanism of action has been validated. Upon positive results from proof-of-concept trials, we intend to pursue additional indications where we believe our product candidates' mechanisms may be relevant, to maximize the potential for each product candidate.
- ***Maximize and protect value through a strong global intellectual property portfolio.*** We have a rigorous strategy to establish and protect the intellectual property rights for our programs, all of which are wholly owned, to allow us to maximize the therapeutic and commercial potential of our pipeline. This strategy includes seeking patent protection in the United States and other jurisdictions for our product candidates, each of which is an NCE. Our portfolio includes numerous filings with multiple different sets of claims that cover proprietary aspects of our lead programs and their use. For ETX-810 and ETX-155, we have issued patents in the United States with coverage to at least 2037 and 2039, respectively, as well as a wide variety of pending applications for these programs in the United States and elsewhere. We continue to leverage new discoveries in the development of these programs to strengthen the breadth and depth of our intellectual property.

Our Strategy

To execute our approach, we plan to implement the following key strategies:

- ***Advance ETX-810 through clinical trials for DPNP and LSRP and progress toward commercialization***. ETX-810 represents a compelling opportunity to develop a novel molecule for the treatment of chronic pain conditions, with a mechanism of action supported by a robust body of precedent clinical research across multiple pain settings. We have completed a Phase 1 single ascending dose and multiple ascending dose trial for ETX-810 in healthy volunteers and are currently executing two randomized placebo-controlled Phase 2a clinical trials aimed at establishing clear proof-of-concept for ETX-810 in DPNP and LSRP. We intend to announce topline data from both Phase 2a clinical trials in 2022. With positive results from these trials, we intend to progress development of ETX-810 into later-stage trials in the United States and other countries to support filings for regulatory approval in key markets.
- ***Advance ETX-155 through clinical trials in both depression and epilepsy indications and progress toward commercialization.*** ETX-155 is a potentially differentiated $GABA_A$ PAM candidate with dual potency at synaptic and extrasynaptic receptors, an approximate 40-hour half-life and no clinically meaningful food effect. We have completed a Phase 1 single and multiple ascending dose trial for ETX-155 in healthy volunteers, and assuming FDA clearance of our IND, we plan to initiate Phase 2a clinical trials in both MDD and PMD in the first half of 2022. In addition, we are evaluating ETX-155 in a Phase 1b photosensitive epilepsy proof-of-concept trial with an interim data readout expected in the first half of 2022. Assuming the results of this trial are positive, we plan to initiate a Phase 2 clinical trial in patients with focal onset seizures in the first half of 2023. With positive results from these trials, we intend to progress development of ETX-155 into later-stage trials in the United States and other countries to support applications for regulatory approval in key markets.
- ***Continue to innovate and advance our preclinical programs into clinical trials in multiple neuronal excitability indications.*** We are currently developing two preclinical-stage programs: (1) a novel Kv7.2/3 channel opener for potential treatment of pain, epilepsy, and depression; and (2) a novel 2,3-benzodiazepine anxiolytic for the potential treatment of generalized anxiety disorder and depression. Both preclinical programs are based on clinically validated mechanisms of action with prior approved molecules in the class. Our aim is to discover and develop proprietary NCEs that improve upon first-generation molecules based on our novel chemical insights and in-depth understanding of the biology and selectivity required to yield drugs with favorable safety and efficacy profiles. We anticipate commencing IND-enabling studies for our Kv7.2/3 program in 2022, and continuing to progress preclinical development of our next-generation anxiolytic in 2022.

- ***Apply our expertise to expand our lead programs into additional indications representing large markets.*** Our team includes established industry leaders in the fields of neuroscience and pain. Through our clinical trials, we intend to enhance our understanding of the mechanism of action for our specific product candidates, and in general our understanding of the biological pathways leading to neuronal inhibition and excitation imbalances to maximize the value of our product candidates. Utilizing this enhanced understanding informed by our initial clinical trials, we plan to evaluate additional potential indications for both ETX-810 and ETX-155. For ETX-810, we will explore additional pain indications, which could enable a broad label in peripheral neuropathic pain and chronic pain. For ETX-155, we intend to explore a wide-range of compelling opportunities in both psychiatry and neurology, including potentially generalized anxiety disorder and bipolar disorder.
- ***Pursue regulatory approvals for our product candidates and commercialize them in key markets.*** We plan to build a fully integrated biotechnology company capable of executing registrational trials, obtaining regulatory approvals and commercializing our drugs globally. We expect to build a focused and efficient medical affairs and commercial organization to help bring our product candidates to patients around the world. Given the potential broad applicability of our product candidates in large patient populations globally, we may also opportunistically enter strategic partnerships with reputable biopharmaceutical companies, with established presence in key geographies, to address the unmet needs of patients worldwide and maximize the overall value of our product candidates.

Our Team

Since commencing operations in 2019, we have assembled a seasoned management team with expertise in neuroscience research and development, medicinal chemistry, clinical development, regulatory affairs, manufacturing and commercialization. Our team includes industry veterans with leadership experience at leading biopharmaceutical companies such as Amgen, Biogen, GSK, Bayer, Novartis and Pfizer, as well as at successful small biotechnology companies such as Alder BioPharmaceuticals, Convergence Pharmaceuticals, Cavion, Exelixis and Juno Therapeutics. In addition, our team has collectively driven development and operational efforts supporting the approval of multiple drugs in chronic pain, depression and epilepsy, including Aptiom, Geodon, Lamictal, Lyrica, Neurontin, Trobalt and Vyepti. Our leadership team's track record of success enables us to continue to recruit highly experienced personnel. Our board of directors is comprised of industry leaders with senior leadership experience at large pharmaceutical organizations and public and private biotechnology companies, bringing significant expertise across neuroscience research and development, corporate governance, finance, organizational strategy and capital raising. Together, we bring years of experience combined with the resilience needed to confront challenging diseases of the nervous system.

ETX-810

We are developing ETX-810, a novel prodrug of PEA, as a treatment for patients suffering from chronic pain. PEA, the active moiety of ETX-810, is an endogenous bioactive lipid known to broadly modulate neuroinflammation and pain signaling. Dietary supplement PEA has shown activity in more than 30 clinical studies across a variety of pain indications, including demonstrating statistically significant reductions in pain in 13 randomized, controlled trials, along with favorable tolerability data. However, there are no FDA or EMA approved PEA-based therapeutics, as no agent has ever been taken through a rigorous clinical development program with a view to obtain regulatory approval. In addition, the only currently available versions of PEA are dietary supplement formulations that, while demonstrating promising clinical activity and tolerability in prior studies, have low bioavailability and overall poor drug-like properties.

ETX-810 was designed to significantly improve the systemic exposure of PEA to explore its full therapeutic potential and to significantly reduce chronic pain. In our Phase 1 clinical trial, ETX-810 demonstrated encouraging safety and tolerability data with all adverse events (AEs) being mild and transient. We believe the endogenous nature of PEA makes ETX-810 unlikely to have drug-drug interactions and limits the potential for abuse liability. We are currently conducting Phase 2a clinical trials of ETX-810 in two chronic pain indications: DPNP and LSRP.

Overview of Chronic Pain and the Unmet Need

Chronic pain is one of the most common and complex conditions in the world and continues to be poorly addressed by available therapeutic options. In the 2016 Global Burden of Disease Study, pain and pain-related conditions were confirmed to be the leading cause of disability and disease burden globally, and this burden is escalating. In patients who are receiving a first line agent for chronic pain, currently approved medications, including Lyrica and Cymbalta, have demonstrated pain intensity reductions of 50% or more in less than 50% of patients. In addition to inadequate efficacy, the current standard of care is hindered by dose-limiting side effects, including dizziness, sedation, gastrointestinal disturbances, as well as concerns over the abuse liability of the opioid class of pain treatments. These limitations of currently approved therapies ultimately lead treating physicians to resort to polypharmacy, prescribing a combination of multiple drugs at once. Despite a massive global chronic pain prescription therapeutics market, there is a high unmet need for safe, effective, non-opioid therapies to treat chronic pain. We believe a significant commercial opportunity exists for a new chronic pain agent with proven efficacy and a favorable safety and tolerability profile.

PEA Proposed Mechanism of Action in Neuroinflammation and Chronic Pain

PEA is an endogenous bioactive lipid that was first described in 1957, but its mechanism of action remained unclear until the 1990s, when the work of Nobel laureate Rita Levi-Montalcini was published describing PEA as part of a class of endogenous regulatory molecules called N-acylethanolamines, which control mast cell activation *in vivo*. Systemically administered N-acylethanolamines were found to be effective in reducing mast cell degranulation and therefore have anti-inflammatory effects. Subsequent preclinical studies have since evaluated these powerful anti-inflammatory effects and revealed analgesic effects of PEA. Evidence demonstrated that PEA acts as a modulator of neuroinflammatory processes. In pathological settings such as chronic pain conditions, PEA production may be insufficient to regulate the inflammatory cascade that downstream drives an increase in pain signaling, and exogenous administration of PEA might prove therapeutically beneficial.

As described in Figure 2 below, PEA's mechanism is considered pleiotropic, as literature supports that it acts through a series of direct and indirect actions involving several effector cells and molecular targets. It is believed that PEA plays a key role as a master regulator of neuroinflammatory processes, triggering multiple signaling cascades to control downstream pain signaling and elicit its potent analgesic effect.

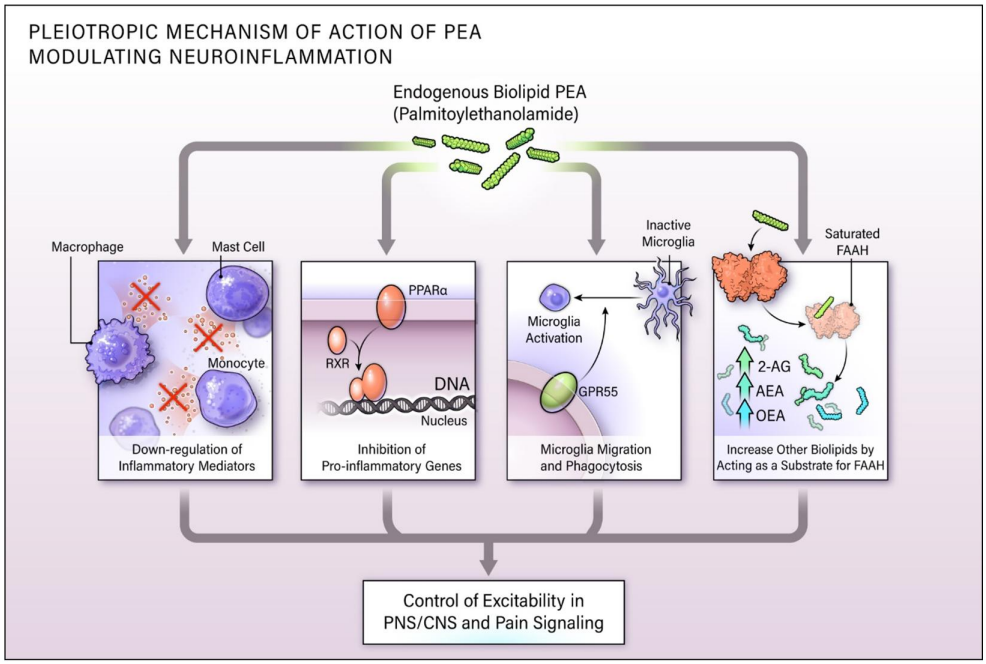

Figure 2. Potential pleiotropic mechanism of action of endogenous PEA for the control of neuroinflammation and neuronal excitability, and therefore downstream pain signaling.

We believe there are multiple aspects of PEA's potential pleiotropic mechanism that remain to be elucidated, but several potentially important mechanisms that have been published include:

1. Inhibition of mast-cell activation and degranulation and downregulation of release of inflammatory mediators from multiple immune cell types;
2. Agonism of the nuclear receptor PPAR-alpha, leading to regulation of expression of several genes, including an inhibition of pro-inflammatory genes;
3. Agonism of the orphan G-protein coupled receptor GPR55, potentially playing a role in microglial cell migration, activation and increased phagocytosis; and
4. An "entourage effect" where PEA increases the level of other endocannabinoids with potential anti-inflammatory and analgesic properties, such as 2-AG, anandamide, and OEA, by acting as a substrate for FAAH.

Figure 3 describes our current understanding of how fluctuations in PEA levels may lead to dysregulation of neuroinflammation and pain signaling. In chronic pain (center panel), evidence demonstrated that there may be both a decrease in PEA synthesis and an increase in PEA metabolism leading to a net decrease in PEA below the level needed to maintain control of neuroinflammation. As a result, sensitization in both the peripheral and central nervous system lead to an increase of pain signaling and pain sensation, relative to a healthy physiological state (left panel of Figure 3). ETX-810 is designed to deliver exogenous PEA and restore PEA to levels needed to reduce neuroinflammation and restore a healthy physiological state, where hyperexcitability of the pain signaling network is dampened and chronic pain is reduced (right panel of Figure 3).

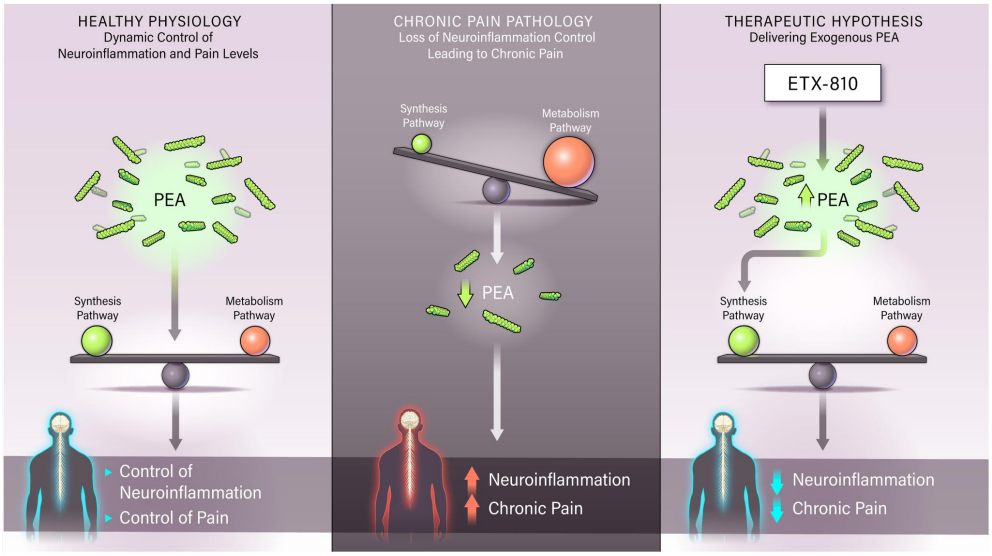

Figure 3. The potential role of PEA in controlling neuroinflammation and pain in normal physiology versus chronic pain states, and therapeutic hypothesis. ETX-810 provides an exogenous source of PEA aimed at rebalancing the body's PEA levels that have been reduced due to an imbalance between synthesis and metabolism of endogenous PEA.

In addition to the preclinical evidence of a decreased level of PEA in chronic pain, a clinical publication further supports the finding in osteoarthritis and rheumatoid arthritis patients showing significantly lower PEA levels in the synovial fluid compared to healthy volunteer control subjects. This data is depicted in Figure 4 below:

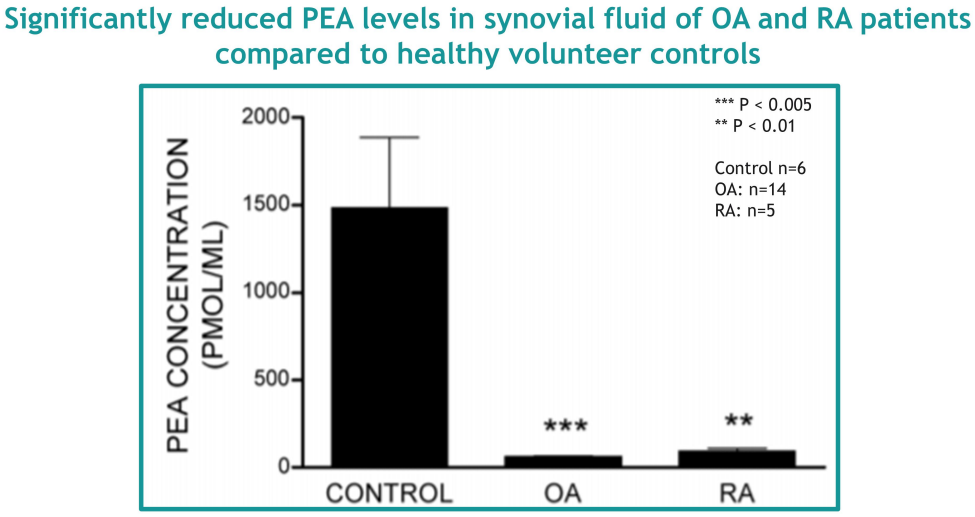

Figure 4. Decreased levels of PEA in the synovial fluid of patients with osteoarthritis (OA), and rheumatoid arthritis (RA) compared to healthy normal volunteers (control); (P <0.005, and P<0.01, respectively). Figure adapted from Richardson et al. Arthritis Res Ther, 2008;10(2):R43.

Clinical Experience with PEA in Pain

The pain-relieving properties of PEA in human diseases associated with chronic pain have been evaluated in multiple clinical studies since the 1990s using PEA in dietary supplement formulations. Over 30 clinical studies, including fifteen randomized, placebo-controlled studies, have been conducted with these dietary supplement formulations across multiple pain indications. Statistically significant reductions in pain intensity were observed in nearly all of these studies with PEA treatment. These studies reported few dropouts and few reported AEs, suggesting that PEA was generally well tolerated. A summary of the fifteen published randomized controlled clinical studies conducted with PEA in various pain conditions, including the PEA dose levels evaluated, is below:

Reference	Pain Condition	Dosing Period	PEA dosing	Other concomitant therapies	Control	N	N in PEA arm(s)
Canteri et al, *DOLOR*, 2010; 25(4):227-234	Lumbar sciatica	21 days	300 mg/day 600 mg/day	NSAIDs	placebo	111	55
Guida et al, *DOLOR*, 2010; 25(1):35-42	Lumbar sciatica (including lumbar radiculopathy)	21 days	300 or 600 mg/day	only continued therapies for comorbidities	placebo	636	427
Bacci et al, *ISRN Surg*, 2011; 2011:917350	Molar extraction pain	15 days	600 mg/day	None	Non-treated extraction	26	26
Cobellis et al, *Eur J Obstet Gynecol Reprod Biol*, 2011; 158(1):82-6	Chronic pelvic pain (endometriosis)	3 months	800 mg/day	polydatin 80 mg/day	1) placebo 2) celecoxib	61	21
Marini et al, *J Orofac Pain*, 2012; 26(2):99-104	TMJ osteoarthritis or arthralgia	2 weeks	900 mg/day wk 1, 600 mg/day wk 2	None	ibuprofen (1800mg/day)	24	12
Murina et al, *J Low Genit Tract Dis*, 2013; 17(2):111-6	Vestibulodynia	60 days	800 mg/day	polydatin 80 mg/day	placebo	20	10
Tartaglia et al, *J Pediatr Adolesc Gynecol*, 2015; 28(6):447-50	Dysmenorrhea	10 days	400 mg/day	polydatin 40 mg/day	placebo	220	110
Orefice et al, *Neurotherapeutics*, 2016; 13(2):428-38	Pain in relapsing-remitting multiple sclerosis	12 months	600 mg/day	IFN-β1a 4 µg (3x/wk)	placebo (+ IFN-β1a)	29	15
Andresen et al, *Pain*, 2016; 157(9):2097-2103	Spinal cord injury neuropathic pain	12 weeks	1200 mg/day	paracetamol (56%), gabapentin (53%), baclofen (31%), strong opioids (28%), pregabalin (25%), tramadol (14%)	placebo	73	36
Giammusso et al, *Arch Ital Urol Androl*, 2017; 89(1):17-21	Chronic pelvic pain (prostatitis)	12 weeks	600 mg/day	alpha lipoic acid (300 mg)	saw palmetto extract	44	22
Faig-Marti et al, *J Orthop Traumatol*, 2017;18(4):451-455	Carpal tunnel syndrome	60 days	600 mg/day	None	placebo	61	30
Evangelista et al, *CNS Neurol Disord Drug Targets*, 2018; 17(4):291-298.	Carpal tunnel syndrome	90 days	1200 mg/day	None	surgery	42	22
Ottaviani et al, *Clin Oral Investig,* 2019; 23(6):2743-2750	Burning mouth syndrome	60 days	1200 mg/day	None	placebo	29	15
Steels et al, *Inflammopharmacology*, 2019; 27(3):475-485	Knee osteoarthritis	8 weeks	300 mg/day 600 mg/day	None	placebo	111	71
Isola et al, *Clin Oral Investig*. 2021 Mar; 25(3):1035-1045	Periodontitis pain	5 days	1600 mg/day	baicalin extract	SRP procedure	66	33

Meta-analyses demonstrated PEA's consistent therapeutic effects

Two meta-analyses have examined the effects of PEA on pain across clinical studies. The most recent meta-analysis of eight randomized, controlled studies by Artukoglu and colleagues in 2017 included a total of 743 patients receiving PEA and 460 inactive controls. Doses used in these trials ranged from 300 to 1200 mg/day and trial durations from 15-180 days. The meta-analysis demonstrated that PEA was associated with a significantly greater pain reduction based on VAS scores compared to control conditions, with a weighted mean reduction in pain score on a 10-point scale of 2.03 (95% CI: 1.19-2.87). A summary of these results is below in Figure 5:

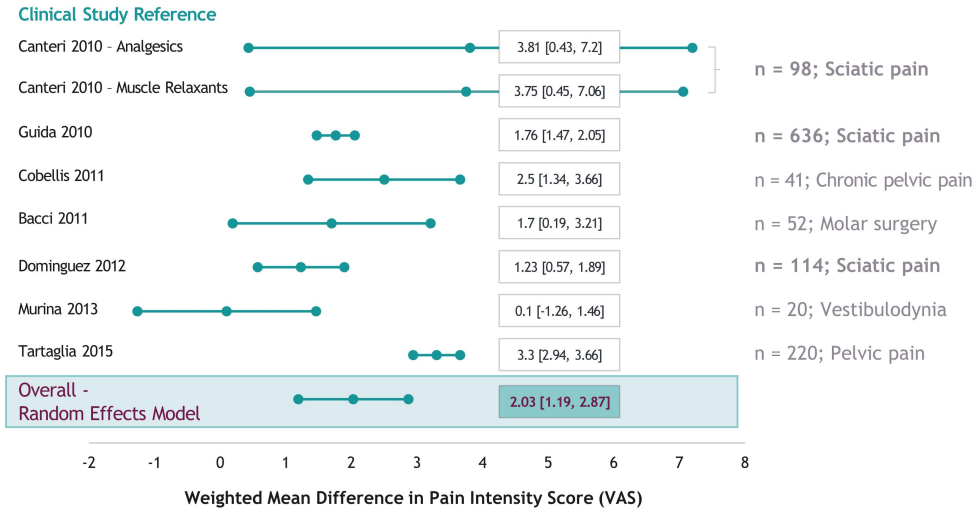

Figure 5. Meta-analysis of randomized clinical trials of PEA in a dietary supplement formulation. Adapted from Artukoglu et al. Pain Physician, 2017;20:353-362.

The weighted mean difference in pain score for PEA vs inactive control of 2.03 from this meta-analysis compares favorably to the standardized mean difference in pain score from meta-analyses conducted on randomized trials of pregabalin and duloxetine, as shown in Figure 6 below:

Drug	Indications studied in meta-analysis	Total subjects	Standardized mean difference in pain score*	Reference
Duloxetine	Osteoarthritis	1713	0.38	Osani and Bannuru, Korean J Intern Med, 2019;34(5):966-973
Duloxetine	Osteoarthritis and chronic low back pain	3098	0.67	Weng et al, Osteoarthritis Cartilage. 2020;28(6):721-734
Duloxetine	Chronic low back pain	851	0.8	Enomoto et al, J Pain Res, 2017;10:1357-1368
Pregabalin	Neuropathic pain (various indications)	6087	0.49	Onakpoya et al. BMJ Open, 2019;9(1):e023600
Pregabalin	Diabetic peripheral neuropathy pain	1897	0.73	Parsons et al., Curr Med Res Opin, 2016;32(5):929-37
Pregabalin	Diabetic peripheral neuropathy pain	2056	0.79	Zhang et al, Acta Anaesthesiol Scand, 2015;59(2):147-59

*Figure 6. Summary of mean pain score reduction from meta-analyses conducted for duloxetine and pregabalin in different chronic pain indications. * shown as absolute value of weighted/standardized pain score reduction compared to placebo.*

PEA's dose-dependent therapeutic effect and impact on neuropathic pain in clinical studies

We believe the most compelling clinical data for PEA in pain come from a multicenter, randomized controlled study that enrolled a total of 636 subjects across nine sites with compressive-type lumbar sciatica who were treated with either 300 or 600 mg dietary supplement PEA (Normast, Epitech) per day, or placebo, for 21 days. The reduction in pain intensity was assessed based on VAS score, and the improvement in health status of patients was evaluated by the Roland-Morris Disability Questionnaire (RMDQ). A dose-dependent effect on both VAS and RMDQ scores was observed. The effect size was statistically significant ($p < 0.001$) on both VAS score (change versus baseline pain scores of 5.0 on 600 mg, 2.9 on 300 mg and 2.0 on placebo) and RMDQ score (change versus baseline of 9.2 on 600 mg, 5.0 on 300 mg and 3.0 on placebo).

Cruccu et al. performed a post-hoc analysis from the raw data associated with the aforementioned study, which was published in 2019. In this analysis additional measures of the clinical efficacy, such as 50% responder rate (VAS pain scores and disability RMDQ scores) and number needed to treat were conducted. In the 600 mg PEA cohort, 82% of patients achieved a 50% or greater reduction in pain intensity as measured by the VAS, as compared to 33% of patients in the 300 mg cohort and 22% of patients in the placebo group. Of patients in the 600 mg PEA cohort, 88% achieved a 50% or greater improvement in physical disability as measured by RMDQ, as compared to 38% in the 300 mg cohort and 23% of patients in the placebo group. In addition, the authors calculated the Numbers-Needed-to-Treat (NNT) to be 1.7 for the 600 mg dose (NNT in this case is defined as the number of patients needed to treat to find one patient who achieves a 50% reduction in pain intensity). This compared very favorably to the NNT of pregabalin and duloxetine published in a meta-analysis of randomized controlled trials in neuropathic pain, where the NNT for 50% pain relief for these drugs was calculated to be 7.7 and 6.4, respectively. Across all measures, 600 mg PEA performed better than 300 mg, suggesting a dose-dependent response and supporting our prodrug approach to increase PEA exposures. These results are summarized in Figure 7 below:

	Placebo	PEA 300 mg	PEA 600 mg
Percent of subjects with ≥50% Pain Relief (VAS)	**22.0%** (46/209)	**33.0%** (70/212)	**81.9%** (176/215)
Percent of subjects with ≥50% improvement in physical disability (RMDQ)	**22.5%** (47/209)	**38.2%** (81/212)	**87.9%** (189/215)
NNT for ≥50% Pain Relief (PEA vs placebo)	-	**9** (CI: 4-14) P<0.005	**1.7** (CI: 1.4-1.7 P<0.0001

Figure 7. Results of a post-hoc analysis of the largest PEA clinical trial conducted to date: a randomized, placebo-controlled trial by Guida et al. in 636 patients with chronic low back pain. Figure adapted from Cruccu et al. CNS & Neurological Disorders – Drug Targets, 2019;18(6):491

In addition, Cruccu et al. developed an ordinal scale to categorize each patient's pain into 5 different groups based on increasing probability of the pain being neuropathic. A significant positive correlation was found between an improvement in pain score and an increasing probability of the pain being neuropathic in nature. This, together with the anti-neuroinflammatory mechanism of action, further supports the hypothesis of using PEA in patients with neuropathic pain.

Another clinical study of PEA as a dietary supplement in osteoarthritis was published by Steels et al. in 2019. In this single site, randomized, controlled study, 111 subjects with osteoarthritis in one or both knees were randomized to receive either 300 mg PEA (n=36), 600 mg PEA (n=35), or matched placebo capsules (n=40), daily for 8 weeks. All participants were required to have a minimum pain level of 4 on the Numerical Rating Scale (NRS) and were not allowed to take any pain concomitant therapies while on study other than paracetamol (acetaminophen) as a rescue therapy. The primary endpoint of the trial was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), which measures pain, stiffness and function. The secondary endpoint was pain intensity measured by the NRS pain scale. All 3 components of the WOMAC score were statistically significantly reduced for both 300 mg and 600 mg PEA groups compared to placebo at week 8. In addition, there was an apparent dose-dependent effect as the 600 mg PEA dose outperformed the 300 mg PEA dose across all metrics evaluated, although the study was not powered to show statistical significance between these two dose levels (Figure 8). There were no SAEs reported in any of the study participants.

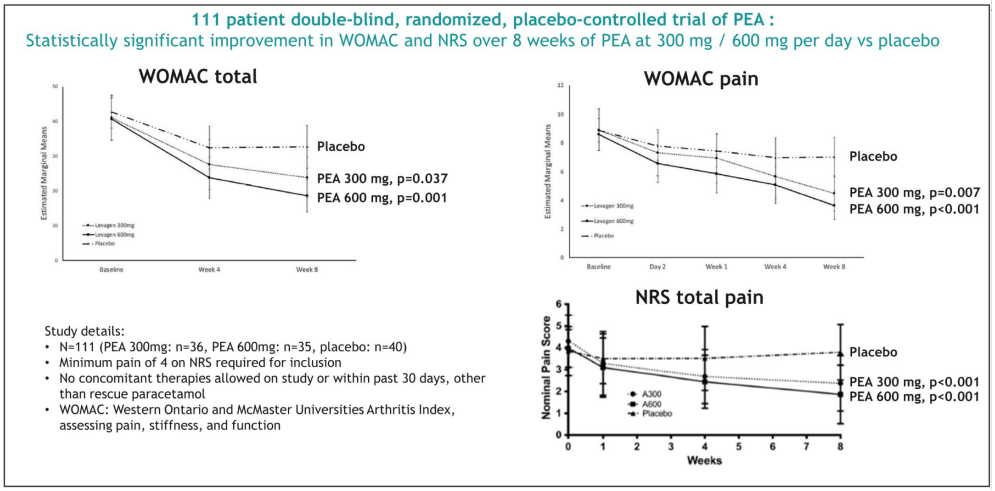

Figure 8. Modified from Steels et al. study (Inflammopharmacology, 2019;27:475-485)—Reduction of WOMAC osteoarthritis total index score, WOMAC pain score and NRS average pain score and WOMAC over 8-week course of treatment with 300 mg/day PEA, 600 mg/day PEA, or placebo.

Both the Guida and Steels studies suggest that an increase in PEA dose may lead to a potential additional clinical benefit in terms of pain reduction, supporting our hypothesis for development of ETX-810 delivering around 3-fold higher PEA exposure than PEA itself (dietary supplement formulation, Normast).

Limitations of PEA pharmacokinetics and our solution

Despite PEA's evaluation in pain indications in numerous clinical trials, there is minimal information available on the pharmacokinetic profile of dietary supplement PEA formulations in humans. Given its lipidic nature and large particle size, PEA in its native state is expected to have limitations in terms of solubility, absorption and bioavailability. While micronized and ultra-micronized nutraceutical formulations of PEA have aimed to improve the bioavailability compared to the native state by reducing the particle size, we are not aware of any published data demonstrating definitive improvement in bioavailability or other pharmacokinetic parameters in humans.

We believe the dose-dependent clinical efficacy and limited number of treatment-related adverse events in precedent clinical studies of PEA in chronic pain provides compelling evidence of the therapeutic potential of PEA. We also believe this supports our approach to develop ETX-810 as an NCE PEA prodrug with desirable pharmacokinetics to explore the full therapeutic potential in patients with chronic pain.

We believe that, if approved by the FDA, ETX-810 may have regulatory and commercial advantages over dietary supplement formulations of PEA, as a PEA-based prescription medicine with regulatory approval for use in the treatment of certain chronic pain indications. We believe these advantages are important differentiating features and considerations for patients and physicians as they evaluate potential treatments. These potential advantages for any FDA approved prescription PEA drug could include:

- *Rigorous regulatory review of NDA including FDA benefit-risk assessment and review of data from clinical studies and chemistry manufacturing and controls information, evaluating safety and effectiveness for use in chronic pain indications.*
- *Ability to provide prescribers with a package insert including robust details on clinical results in the specific patient populations (such as DPNP and LSRP) studied in our clinical studies including efficacy, safety, recommended dosing, pharmacokinetics, long-term safety, and any potential drug-to-drug interactions.*
- *Ability to market with claims regarding treatment effect on certain chronic pain indications, to the extent permitted under an FDA-approved label.*
- *Obligations to manufacture, assure quality control and distribute in accordance with pharmaceutical cGMP requirements*.
- *Potential for coverage and reimbursement by third-party payors*.

ETX-810 Competitive Advantages

We believe that ETX-810 offers several key differentiating features compared to currently available therapies for chronic pain.

- *Novel approach to chronic pain with demonstrated clinical proof of concept.* ETX-810 is believed to be the only PEA prodrug in clinical development and is being developed based on precedent clinical studies of dietary supplement formulations of PEA that demonstrated clinically meaningful statistically significant reductions in pain intensity in over 12 randomized placebo clinical trials. These trials collectively included approximately 1,500 patients spanning multiple inflammatory and neuropathic chronic pain conditions. In one study of over 600 chronic low back pain patients, PEA demonstrated statistically significant reductions in pain versus placebo including a greater than 50% reduction in pain intensity in 82% of patients. Published studies suggest that first line agents for chronic pain, such as the currently approved medications Lyrica and Cymbalta, are able to provide substantial pain relief (a reduction in pain score of 50% or more) in less than 50% of patients. Building upon the strength of these clinical data, we believe ETX-810 has the potential to be the first PEA-based therapeutic to address the unmet need in the large chronic pain market, although cross-trial comparisons may not be reliable predictors of the relative efficacy or other benefits that ETX-810 may have compared to other product candidates that may be approved or that are in development.
- *Designed for desirable pharmacokinetics.* Commercially available formulations of PEA are currently only available as dietary supplements and have low bioavailability with overall poor drug-like properties, likely leading to suboptimal exposures. ETX-810 was designed to significantly improve the systemic exposure of PEA in order to maximize the therapeutic effect. ETX-810 was observed, in preclinical studies, to be rapidly absorbed after oral administration and to undergo enzymatic hydrolysis during absorption and in plasma to efficiently release high concentrations of free PEA. In clinical studies in a small number (80) of healthy volunteers, ETX-810 has demonstrated rapid absorption and efficient release of biologically active PEA, resulting in approximately three times higher PEA exposure on a matched dose basis compared to a commercially available dietary supplement formulation of PEA, as well as an approximately three to six times longer half-life compared to the published estimated half-life of PEA in rats. Precedent clinical data has demonstrated a clear dose response with respect to PEA's ability to reduce pain intensity in chronic pain settings, which we believe supports our approach to optimize the pharmacokinetic exposure of PEA with ETX-810.
- *Well tolerated and no known abuse liability in clinical studies.* Phase 1 single- and multiple-ascending dose clinical trials with ETX-810 suggest the potential for an encouraging tolerability profile, and clinical trials conducted to date have resulted in no SAEs, no discontinuations, and no clinically meaningful differences from placebo. These findings are consistent with published results from clinical trials conducted with dietary supplement formulations of PEA. In contrast, existing chronic pain therapies are associated with a range of dose-limiting adverse effects including GI problems, drowsiness, dizziness, nausea, somnolence and others. In addition, as an endogenous bioactive lipid, the potential for abuse is considered to be low, potentially addressing the critical unmet need in chronic pain treatment for novel, non-opioid and non-addictive therapeutic options. Prior clinical studies of PEA have no reported adverse events related to abuse.

- *Potential to be used in chronic pain as a monotherapy or in combination with other analgesics.* In multiple prior clinical trials with dietary supplement formulations of PEA, a reduction in pain intensity was observed with PEA in chronic pain both as a monotherapy and when used in combination with other pain therapies such as opioids, antidepressants and anticonvulsants. Because polypharmacy is a common treatment strategy used by clinicians treating chronic pain, the market is in need of therapies that can safely and effectively be used in combination with others. We believe the favorable tolerability data in clinical trials and the endogenous nature of PEA make ETX-810 unlikely to have drug-to-drug interactions and position it for the potential to be used in combination with other chronic pain medications, if approved.

Chronic Pain Indication Overview

Chronic pain, generally described as pain lasting more than three to six months, is one of the most common and complex conditions. It is estimated to affect approximately 20% of adults in the United States and Europe. Despite the high prevalence worldwide, there are few approved medicines to treat chronic pain and the existing therapeutic options suffer from limited efficacy coupled with a range of adverse effects which can limit their utility, reduce compliance and complicate their ability to combine with other drugs. The two initial chronic pain indications we plan to pursue for ETX-810 are pain associated with diabetic peripheral neuropathy (DPNP) and lumbosacral radicular pain (LSRP).

Diabetic Peripheral Neuropathy (DPN)

DPN is a common, late manifestation of diabetes characterized by damage to the sensory and autonomic nervous system caused by prolonged poor glycemic control and increased levels of triglycerides in the blood. Neuropathic pain is associated with DPN, leading to an exaggerated response to painful stimuli (hyperalgesia) and pain evoked by light contact, such as those with shoes or clothing (allodynia). This pain can lead to interference with daily activities, disability, psychosocial impairment and reduced health-related quality of life. While DPN can be managed to slow further progression, its symptoms, including chronic neuropathic pain, are generally not reversible once they emerge. There are significant direct and indirect costs associated with the effects of DPN, with approximately one quarter of health expenditure in diabetes spent on management of DPN.

It is estimated that 30% to 50% of people with diabetes will experience diabetic peripheral neuropathy, and 40-50% of those with DPN will experience DPNP. This provides a prevalence estimate of approximately 5.0 million to 7.0 million DPNP patients in the United States and 9.0 million to 12.0 million in Europe. Of treated DPNP patients it is estimated that 50% to 70% have an inadequate response to first line therapy, leading to an estimated 1.5 million to 3.0 million treatment-refractory DPNP patients in the United States and approximately 2.7 million to 5.0 million DPNP patients in Europe.

There are currently several pharmacological treatments recommended for the first-line treatment (both approved and off-label), to reduce pain and improve quality of life in DPNP patients, including several antidepressants (*e.g.*, duloxetine, venlafaxine, amitriptyline and other tricyclic drugs) and gabapentinoid anti-seizure medications (*e.g.*, pregabalin and gabapentins). Available evidence suggests that all of these treatments are better than placebo in improving DPNP, but few high-quality comparative trials have been carried out, and there are only three products approved by the FDA and EMA for DPNP: duloxetine (Cymbalta), pregabalin (Lyrica) and the opioid tapentadol (Nucynta). For patients with an inadequate response to first line therapy, second line therapy generally consists of switching to a different first-line medication class or combining multiple first-line agents (polypharmacy), though this can be complicated by the risk of compounding adverse effects. Opioids are recommended to help manage pain in DPNP only after all other first/second-line approaches and combinations fail.

DPNP remains an unmet need and is a primary driver of physical and psychological comorbidity. Available therapies for DPNP have moderate efficacy with adverse effects limiting optimal dose titration. In registrational studies of pregabalin and duloxetine, only 40% to 50% of patients achieved a clinically meaningful response of a 50% improvement in pain from baseline, with roughly one quarter of these patients reporting dizziness or nausea adverse events. There is a considerable need for new therapies for the management of DPNP that provide improved efficacy with a more favorable tolerability and safety profile.

We believe that ETX-810, if approved, could potentially be positioned as the preferred second-line monotherapy or add-on agent for the 50% to 70% of DPNP patients who fail to achieve adequate pain relief from generic first-line treatment options, potentially providing improved efficacy versus alternative options and preventing unnecessary opioid usage in this patient group. This represents a target patient population of approximately 4 million to 8 million patients in the United States and Europe.

Lumbosacral Radicular Pain (LSRP)

LSRP is a neuropathic pain syndrome caused by compression, inflammation and or injury of spinal nerve roots in the lower back and is characterized by lower back pain that radiates into the leg in predictable patterns. The leg pain is typically much worse than the lower back pain and is described as being electric, burning or sharp. Additionally, affected people may experience numbness, muscle weakness and loss of specific reflexes. The most common cause of LSRP is nerve root compression caused by a disc herniation or spondylosis (narrowing of the intraspinal canal, the lateral recess, or the neural foramen) due to degenerative arthritis affecting the spine. While LSRP can occur at any age, it often effects men beginning in their 40s and women in their 50s and 60s.

Multiple sources suggest that between 3% and 5% of the adult population is affected by the condition, with equal rates among men and women, which corresponds to approximately 10 million to 16 million people in the United States and 15 million to 26 million people in Europe. Approximately 30% of these patients see their condition progress to chronic, with pain progressing past the three-month mark.

For patients diagnosed with LSRP, the aim of treatment is to alleviate the pain, and if necessary, address the underlying cause of nerve irritation/compression. Patients are initially treated with non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen and modification to physical activity. For patients with continued pain after approximately six to eight weeks of NSAID or acetaminophen treatment, some patients obtain epidural steroid injections, which has been demonstrated to provide short-term pain relief. Patients failing to achieve adequate pain relief may be prescribed gabapentinoids, such as Neurontin and Lyrica. Studies with gabapentinoids in LSRP have demonstrated varying results and a recent meta-analysis found that these agents do not provide effective treatment and are associated with an increased risk of adverse events. Additionally, opioids are used in patients who have severe pain. Many physicians, however, oppose opioid use in LSRP as there is a lack of high-quality data supporting their use for this condition. Furthermore, the use of opioids is associated with adverse events and the potential for abuse.

Due to the limited efficacy and potential side effects of current treatments, there continues to be a need for effective, non-opioid therapies for the treatment of LSRP. We believe that ETX-810 could potentially be positioned as the preferred second line monotherapy or add-on agent over epidural steroid injections or opioids in those patients who fail to achieve adequate relief with NSAIDs or acetaminophen. This represents an estimated target patient population of approximately 7.5 million to 12.5 million LSRP patients in the United States and Europe.

ETX-810 Clinical Development

We have evaluated the safety and tolerability of ETX-810 in 68 individuals across two completed Phase 1 clinical trials. ETX-810 was well tolerated and all AEs were mild and transient. We are currently enrolling proof-of-concept Phase 2a clinical trials in patients with DPNP and LSRP.

Phase 1 SAD and MAD Clinical Trials in Healthy Volunteers

The first clinical trial conducted with ETX-810 was a combined single ascending dose (SAD) and multiple ascending dose (MAD) trial in healthy volunteers. Fifty subjects in the SAD portion of the trial received single doses of either placebo or ETX-810 ranging from 50 mg to 1200 mg and 20 subjects in the MAD portion received repeated doses of either placebo or ETX-810 at 500 mg and 1000 mg administered twice daily for seven days.

The SAD portion of this trial enrolled five cohorts of 10 participants, who each received single doses of ETX-810 ranging from 50 mg to 1200 mg; participants were randomized 4:1 ETX-810 to placebo. All cohorts were dosed in a fed state except the 50 mg and 150 mg fasted cohorts. The participants in the 150 mg cohort were dosed in both a fed and a fasted state, 5 days apart, to assess the effect of food on absorption.

There were no clinically significant changes nor trends across dose groups seen in vital signs, ECG, blood chemistry, hematology, nor urinalysis; a single adverse event (AE) (headache) required treatment (ibuprofen). There was no difference in the incidence of AEs among dose groups and no trends toward an increase in incidence with increasing dose. With respect to pharmacokinetics, ETX-810 was found to convert rapidly to its hydrolysis intermediates and to PEA and was found to be more completely absorbed when administered with food. The results of the SAD portion of the trial justified the selection of 500 mg and 1000 mg as the doses for the MAD portion of the trial.

The MAD portion of this trial enrolled two cohorts with 10 participants in each. In each cohort, eight participants were administered active investigational product and two were administered a placebo twice daily for six days with a single dose administered on Day 7. Participants in cohorts 1 and 2 received 500 mg and 1000 mg ETX-810, respectively, or placebo following food. The interval between the two daily doses was 12 hours.

Treatment was well tolerated; there were no clinically significant changes nor trends across dose groups seen in vital signs, ECG, blood chemistry, hematology, nor urinalysis. No AEs required treatment or led to interruption or discontinuation of treatment. A single AE (insomnia) was rated moderate; all others were mild. There was no difference in the incidence of AEs among groups, and no trend to an increase in incidence with increasing dose. Figure 9 describes the percentage of subjects with adverse events from the ETX-810 SAD and MAD portions of the trial.

SAD Study (n=60)

Adverse Event	Placebo (n=12)	ETX-810 (50-1200mg) (n=48*)
Any AE	33%	29%
Somnolence	8%	10%
Dizziness	0%	8%
Headache	0%	4%
Disorientation	0%	2%
Euphoric mood	0%	2%
Paraesthesia	0%	2%
Nausea	17%	6%
Diarrhoea	0%	2%
Dry mouth	0%	2%
Dyspepsia	8%	0%
Fatigue	17%	2%
Pallor	0%	2%
Palpitations	0%	2%

* same subjects participated in both the 150mg fasted and fed dosing conditions

MAD Study (n=20)

Adverse Event	Placebo (n=4)	ETX-810 500mg BID (n=8)	ETX-810 1000mg BID (n=8)
Any AE	50%	38%	38%
Nausea	25%	0%	25%
Vomiting	25%	0%	0%
Menorrhagia	0%	25%	0%
Dysmenorrhea	0%	13%	0%
Insomnia	0%	13%	0%
Headache	25%	0%	13%
Dizziness	0%	0%	13%
Muscle twitching	0%	0%	13%
Muscle spasms	0%	0%	13%

- Participants were dosed every 12 hrs for 6 consecutive days; a single dose was administered on day 7
- All doses were administered following a meal

Figure 9. Percent of subjects reporting adverse events in the ETX-810 Phase 1 study, 011810-101, in the (a) SAD portion of the trial and (b) MAD portion of the trial.

Phase 1 Pharmacokinetic Clinical Trial Evaluating a 500 mg Single-capsule Formulation and Effect of Food

A 500 mg single-capsule formulation was developed to reduce capsule burden. With this formulation, we conducted a second Phase 1 clinical trial (Study 018810-102) evaluating the pharmacokinetics of two dose levels with and without food. Each of the 12 participants received two dose levels of ETX-810 (500 and 1000 mg) with and without food separated by 24 hours in this randomized 4-way crossover. Treatment was well tolerated with adverse events reported consistent with the prior SAD and MAD clinical trials.

In this trial the administration of ETX-810 with food was found to significantly increase the AUC0-24h values for the metabolic intermediates and the active metabolite PEA. ETX-810 concentrations were below measurable quantities at all time points, indicating rapid conversion to its metabolites upon administration. Cmax for these metabolites was not found to be increased when ETX-810 was administered with food compared to the fasted state. Based on these results and the SAD and MAD trials, in future trials ETX-810 will be dosed with food.

Potential Improvement in PEA Exposure from ETX-810 vs Dietary Supplement PEA

We conducted a clinical trial to evaluate a commercially available ultramicronized dietary supplement formulation of PEA in a small number (8) of healthy volunteers in order to establish well-controlled pharmacokinetics to provide a baseline for comparison to ETX-810, given the lack of availability of high-quality human pharmacokinetic data for PEA.

This trial evaluated a single dose of 300 mg or 600 mg of a dietary supplement formulation of PEA (Normast) in eight subjects, with 300 mg tested in both a fasted and a fed state and 600 mg tested only in a fed state, in each case after a five-day washout period between doses. Blood samples were taken prior to and up to 12 hours after each dose. Prior to dosing, endogenous PEA concentrations averaged approximately 4-7 ng/mL and were consistent within and between subjects across dosing periods.

The administration of dietary supplement PEA increased PEA concentrations in all participants at all dosing periods, but with high subject-to-subject variability, particularly with respect to Cmax and Tmax. Administration of the 300 mg dose after a meal resulted in greater increases in PEA than did administrations in the fasted state, with approximately 2-fold higher AUC0-12h and 3-fold higher Cmax.

The plot provided below highlights the comparison of PEA exposure (AUC0-12h) between a single 1000 mg dose of ETX-810 from Study 018810-102 compared to the 600 mg dose of dietary supplement PEA, from Study 018875-101, both in the fed state. Although this comparison was not based on a head-to-head study, a single 1000 mg dose of ETX-810 prodrug (which delivers ~490 mg of PEA) achieved approximately three-fold higher PEA exposure than a 600 mg dose of dietary supplement PEA, which has demonstrated a statistically significant reduction in pain in multiple clinical studies. We believe the increased exposure is potentially driven by improved oral bioavailability, rapid absorption and a longer half-life of PEA when delivered via the ETX-810 prodrug.

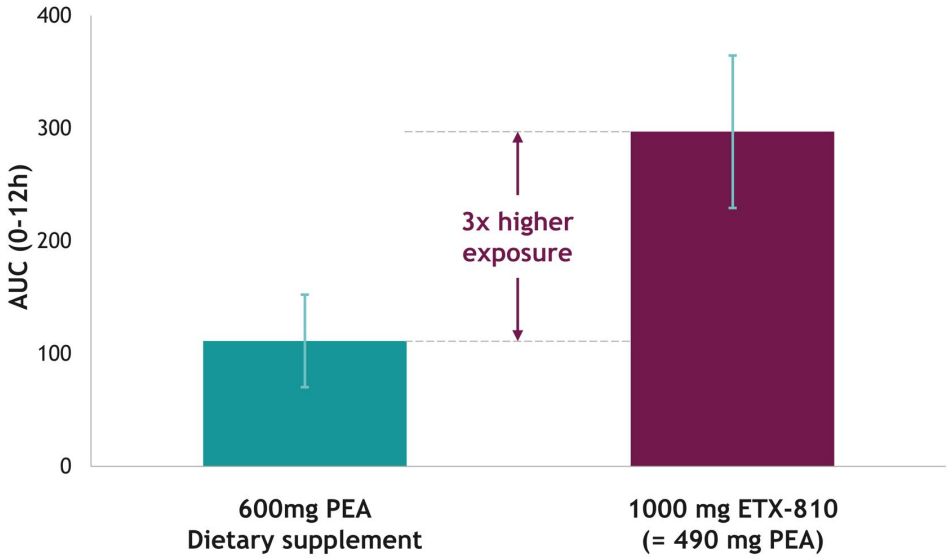

Figure 10. Comparison of exposure of PEA from ETX-810 compared to an ultramicronized dietary supplement formulation of PEA from two different clinical studies. ETX-810 data was taken from the 1000 mg fed cohort of the ETX-810 018810-102 PK trial. Ultramicronized PEA data was taken from the 600 mg fed cohort of the 018875-101 PK trial of dietary supplement PEA. Each 1000 mg capsule of ETX-810 corresponds to ~490 mg of PEA active ingredient.

In our ongoing Phase 2a clinical trials, we are dosing 1000 mg ETX-810 *bis in die* (BID, twice daily) with food, meaning in these trials we are theoretically achieving approximately six times the daily exposure as would be expected from the standard clinical dose (*i.e.*, 600 mg/day) of PEA from dietary supplements. Based on the dose response observed with dietary supplement formulations of PEA in multiple prior studies, we believe that the increased exposure provided by ETX-810 provides us with the possibility to evaluate the full potential therapeutic effect of PEA in chronic pain indications.

ETX-810 is rapidly absorbed and undergoes a series of hydrolysis steps to be converted into the active moiety PEA. Studies have shown that ETX-810 did not have any potential for either direct or time-dependent inhibition of the cytochrome P450 (CYP) isozymes. Because the majority of metabolism of PEA occurs through esterases and lipases, and not through CYPs, there is little to no potential for drug-drug interactions. PEA is further degraded by N-acylethanolamine acid amidase (NAAA) and to a lesser extent by fatty acid amid hydrolase (FAAH) into palmitic acid and ethanolamine. We believe this supports ETX-810's potential as a monotherapy or in combination with other pain drugs.

Phase 2a Clinical Trials

Based on the extensive clinical data on the efficacy of dietary supplement PEA and the findings on tolerability and exposure of our PEA prodrug, ETX-810, observed in our Phase 1 SAD/MAD and pharmacokinetic (PK) trials, we initiated Phase 2a clinical trials in two chronic pain conditions: DPNP and LSRP. Our clinical development team has significant experience designing and running clinical trials in chronic pain, allowing us to implement strategies that attempt to limit the patient-to-patient variability and placebo effect commonly observed in chronic pain studies.

Phase 2a DPNP clinical trial

This Phase 2a clinical trial is a prospective, multi-center, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ETX-810 in adults with DPNP. Patients are instructed to take their study drug, either 1000 mg of ETX-810 or placebo, twice per day, approximately twelve hours apart, with food. The primary endpoint of the trial is the change from baseline to week 4 in the weekly average of the daily pain score on the 11-point PI-NRS. Secondary endpoints include percent of patients with 50% and 30% reduction from baseline to Weeks 1, 2, 3 and 4 in the weekly average of the daily pain score.

A trial schema of the Phase 2a DPNP clinical trial is provided below:

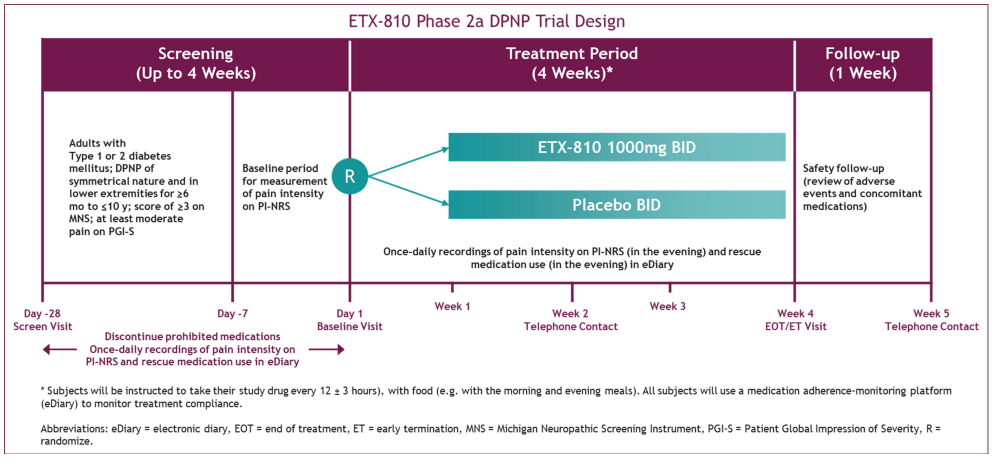

Figure 11. ETX-810 Phase 2a DPNP trial schema

A total of 167 subjects have been randomized in a 1:1 ratio to the ETX-810 or placebo treatment group. An estimated sample size of 81 subjects per treatment group will provide 80% power to detect a 1.0-point change in the mean change from baseline to Week 4 in the weekly average daily pain score on the PI-NRS, with an assumed standard deviation of 2.2, based on previously published studies and clinical experience.

We have fully enrolled this clinical trial, completed dosing and expect to have a topline data readout during the first half of 2022.

Phase 2a LSRP clinical trial

This Phase 2a clinical trial is a prospective, multi-center, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of ETX-810 in adults with LSRP. Patients are instructed to take their study drug, either 1000 mg of ETX-810 or placebo, twice per day, approximately twelve hours apart, with food. The primary endpoint of the trial is the change from baseline to week four in the weekly average of the daily pain score on the 11-point Pain Intensity Numerical Rating Scale (PI-NRS). Secondary endpoints include percent of patients with greater than 50% and 30% reduction from baseline to Weeks 1, 2, 3 and 4 in the weekly average of the daily pain score.

A trial schema of the Phase 2a LSRP clinical trial is provided below:

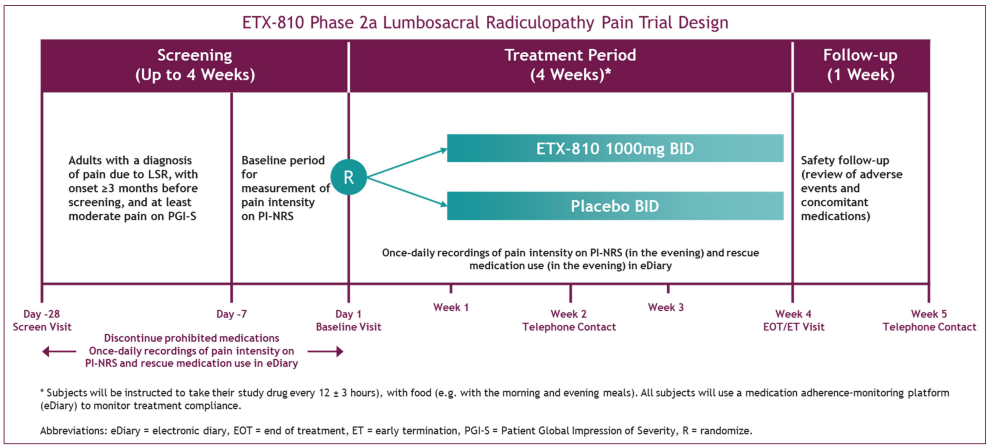

Figure 12. ETX-810 Phase 2a LSRP trial schema

A total of 122 subjects are planned to be randomized in a 1:1 ratio to the ETX-810 or placebo treatment group. A sample size of 61 subjects per treatment group will provide 80% power to detect a 1.0-point change in the mean change from baseline to Week 4 in the weekly average daily pain score on the pain intensity (PI)-NRS, with an assumed standard deviation of 1.9, based on previously published studies and clinical experience.

We are actively enrolling LSRP patients into this clinical trial and expect to fully enroll this study in the first half of 2022 and have a topline data readout during the second half of 2022.

Future Clinical Trials for ETX-810

Based on the results of our Phase 2a clinical trials, we intend to consult with the FDA about future Phase 2b/3 clinical trials. Our current plan is to initiate a Phase 2b dose-range finding trial in DPNP in the second half of 2022 and potentially a second Phase 2b dose-range finding trial in LSRP in the first half of 2023, pending results of the Phase 2a studies and discussion with the FDA. Beyond these initial indications, through careful consideration of our clinical data, the market and competitive landscape, and correspondence with the FDA, we plan to evaluate other opportunities to potentially expand development of ETX-810, which could enable a broad label in peripheral neuropathic pain and chronic pain. In addition, we have initiated a Phase 1 study in healthy human subjects evaluating the pharmacokinetics, safety, and tolerability of two additional high-strength formulations aimed at further optimizing the ETX-810 drug product.

ETX-155

We are developing ETX-155, a $GABA_A$ receptor positive allosteric modulator, or $GABA_A$ PAM, for the treatment of patients suffering from MDD, PMD and FOS. The $GABA_A$ PAM class has been clinically validated in both depression and epilepsy indications by a variety of different agents in the class. ETX-155 was designed to have broad potency across both synaptic and extrasynaptic $GABA_A$ receptor subtypes. ETX-155 has also shown desirable pharmacokinetic properties, including no clinically meaningful food effect and an approximate 40-hour half-life to enable once-a-day-dosing, positioning it favorably within the $GABA_A$ PAM therapeutic class. We believe ETX-155's potent activity across $GABA_A$ receptor subtypes and efficacy in preclinical models of epilepsy, depression, and anxiety supports its application in multiple therapeutic settings. We have initiated a Phase 1b photosensitive epilepsy trial, which if successful, would support initiating a Phase 2 clinical trial in FOS. We plan to announce interim data from the photosensitive epilepsy trial in the first half of 2022. In addition, in the first half of 2022, assuming FDA clearance of our IND filed in the first quarter of 2022 with the psychiatry division, we intend to initiate both a Phase 2a clinical trial in patients with MDD and a Phase 2a clinical trial in patients with PMD, and we expect both trials to report topline data in the second half of 2023.

GABA$_A$ Receptor as a Therapeutic Target for Neurological and Psychiatric Disorders

Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the central nervous system. Neuronal signaling by GABA via the GABA type A receptor (GABA$_A$R) plays a critical role in a wide range of processes within the CNS. Modulation of the GABA$_A$Rs via small molecules has been a highly active area of research since their initial discovery in the 1960s. GABA$_A$R is a clinically validated target, with multiple classes of GABA$_A$R-targeted drugs on the market, including benzodiazepines, anesthetics, anticonvulsants, neuroactive steroids (neurosteroids) and barbiturates.

GABA$_A$Rs are ligand-gated chloride channels with a pentameric structure composed of α, ß, g and d subunits in a 2:2:1 stoichiometry. GABA-induced chloride influx mediated through GABA$_A$Rs leads to hyperpolarization of neurons, preventing action potentials and dampening down neuronal excitability. There are six α, three b, two g and d subunits (also rare e, q and p subunits) that assemble to form 19 GABA$_A$R subtypes. The subunit structures, abundance, distribution and drug binding regions of GABA$_A$Rs are summarized below.

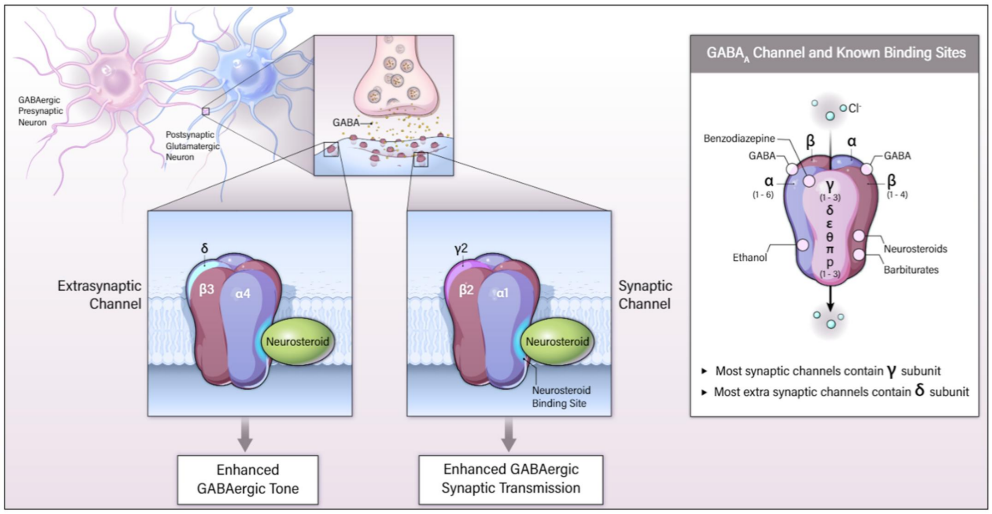

Figure 13. Mechanism of action of neurosteroid positive allosteric modulators (PAMs) of synaptic and extrasynaptic GABA$_A$ receptors. Neurosteroid PAMs can bind to and activate both synaptic and extrasynaptic GABA$_A$ receptors via an allosteric site distinct from the GABA and benzodiazepine binding sites. This potentiates the action of both phasic and tonic inhibitory neurotransmission mediated by GABA$_A$ receptors, leading to decreased neuronal excitability. ETX-155 is an investigational neurosteroid with dual potency at synaptic and extrasynaptic GABA$_A$ receptors.

GABA$_A$ Structure and Properties:

- 19 GABA$_A$ subtypes are differentially expressed in the brain with distinct regional and cellular distribution dependent on subunit compositions
- Of the 19 subtypes, α1 GABA$_A$Rs are the most abundant (60%), with α2 and α3 less abundant (10-20%) and α4 and α5 GABA$_A$Rs the least abundant (~5%)
- α1ßg2, α2ßg2 and α3ßg2 subtypes are expressed predominantly in synapses while α4 and α5 GABA$_A$Rs are primarily extrasynaptic
- The d subunit preferentially pairs with α4, α6 and ß2/3 subunits and these GABA$_A$Rs are also expressed at extrasynaptic sites
- Benzodiazepines act only on synaptic receptors, inducing short term effects
- Neurosteroids bind to a distinct site on both g and d GABA$_A$Rs and regulate both synaptic and extrasynaptic neuron functions

The $GABA_A$Rs are typically clustered opposite GABA-releasing neuronal terminals. The synaptic α1ßg2, α2ßg2 and α3ßg2 subtypes mediate rapid phasic inhibition of nerve action potentials. The extrasynaptic α4, α6 and ß2/3 and d subunit-containing $GABA_A$Rs mediate tonic inhibition, potentially generating a more powerful and broader modulation of cortical neural-network activity that is relevant in multiple CNS disease states and disorders.

Positive allosteric modulators, or PAMs, are substances that bind to a receptor at a distinct site from the primary endogenous ligand and enhance the receptor's response to the ligand. $GABA_A$ PAMs act by enhancing endogenous GABA's activity at these receptors. Allopregnanolone is an endogenous $GABA_A$PAM and fluctuations in allopregnanolone levels are associated with the pathophysiology of mood, anxiety and other psychiatric disorders. Exogenous neuroactive steroids (neurosteroids) are an emerging class of PAMs with potential for treating complex CNS disorders. ZULRESSO (brexanolone/exogenous allopregnanolone; Sage Therapeutics, Inc.) was approved in 2019 for the treatment of postpartum depression (PPD). Other neurosteroid molecules in clinical development include zuranolone (SAGE-217; Sage Therapeutics, Inc.) for PPD and MDD, ganaxolone (Marinus Pharmaceuticals, Inc) for rare epilepsies and PRAX-114 (Praxis Precision Medicines, Inc.) in MDD. CVL-865 (Cerevel Therapeutics, Inc.) is also a $GABA_A$ PAM in clinical development for epilepsy, but unlike the neurosteroids, CVL-865 binds to the benzodiazepine site of synaptic α2/3/5 $GABA_A$R subtypes. The clinical data generated from these candidates suggest that a $GABA_A$ receptor PAM may have potential therapeutic effect in depression and epilepsy. However, pharmacokinetic properties and/or tolerability concerns leave an opportunity for clinical differentiation with ETX-155.

ETX-155 and its Competitive Advantages

ETX-155 is a neurosteroid $GABA_A$ PAM NCE designed to have broad potency at synaptic and extrasynaptic $GABA_A$ receptors (EC50's of 95 – 330 nM). In preclinical studies, ETX-155 showed favorable pharmacokinetic properties and potent activity across several animal models of CNS diseases. Based on these studies, we believe ETX-155 is a promising investigational therapy for treatment of psychiatric mood disorders and focal onset seizures. We believe ETX-155 has several potential advantages that, collectively, differentiate it from other product candidates in the $GABA_A$ PAM therapeutic class and could represent a compelling clinical profile.

- *Dual synaptic and extrasynaptic activity*. ETX-155's design to bind at the synaptic and extrasynaptic $GABA_A$Rs is believed to cause enhanced phasic and tonic inhibition, which can lead to decreased neuronal excitability. We believe that both types of inhibition are important for neurosteroid clinical efficacy in depression and epilepsy, as suggested by the positive clinical results of brexanolone and zuranolone in depression and ganaxolone in epilepsy, all of which have dual activity at synaptic and extrasynaptic $GABA_A$Rs.
- *Consistency of effect*. Phase 1 clinical trials demonstrate that taking ETX-155 with or without food does not result in a clinically meaningful difference in pharmacokinetics, specifically with the Cmax, and the total drug exposure (AUC). This is a unique characteristic in contrast to other $GABA_A$ PAMs such as ganaxolone, brexanolone and zuranolone which are reported to require administration timed with a meal to achieve desired clinical outcomes. Given challenges with patient compliance, we believe the lack of a clinically meaningful food effect is an important patient-centric differentiation that should allow patients the flexibility to take therapy with or without a meal while maintaining a consistent therapeutic exposure.
- *Once a day dosing*. ETX-155 demonstrated a half-life of approximately 40 hours in a Phase 1 study in healthy human subjects, which provides confidence the agent can be utilized in a once-a-day evening dosing regimen. We believe this will be a competitively differentiated and favorable dosing regimen for patients. The pharmacokinetic data for ETX-155 compares favorably with other GABA PAM product candidates in development, which have demonstrated half-lives ranging from approximately 2 hours to 18 hours.
- *Potential for favorable therapeutic window across a broad set of CNS indications*. To date, ETX-155 has shown encouraging safety and tolerability data in its SAD and MAD Phase 1 clinical trials. The exposures attained from the 60 mg dose in our Phase 1 MAD cohorts are consistent with the exposures that led to robust activity of ETX-155 in our preclinical models of depression, anxiety and epilepsy. This increases our confidence that 60 mg has the potential to be an efficacious dose in the indications we are pursuing. Separately, we believe the favorable tolerability data demonstrated in our SAD and MAD clinical trials and the activity observed in preclinical models will support our evaluation of a range of doses to potentially offer physicians different dose levels, allowing for patient-centric dosing.

Major Depressive Disorder (MDD)

MDD is a long-term, sometimes lifelong mood disorder capable of causing severe impairments that interfere with the ability to carry out life activities. MDD is a recurrent disease and follows a fluctuating course of depressive episodes over an individual's lifetime, with periods of remission and relapse. MDD episodes are characterized by periods of at least two weeks of persistent depressed mood and/or the loss of interest in activities, accompanied by symptoms such as sleep and appetite disturbance, fatigue, concentration difficulty, cognitive impairment, feelings of guilt, agitation and suicidal ideation. The 12-month prevalence of MDD in 2020 was estimated to be 35 million across the major markets of the United States, Europe and Japan. It was also recently reported that serious depression symptoms have increased by more than 3-fold overall during the COVID-19 pandemic, though the long-term impact of the pandemic on the prevalence of MDD remains to be determined.

MDD is difficult to treat, with current approaches utilizing a "trial-and-error" sequential treatment strategy because there are no consistently identified predictors of differential response across treatment modalities. The most used current therapeutic treatments for MDD include mixed SNRIs and SSRIs, dopaminergic/noradrenergic agents and atypical antipsychotics. Nearly two thirds of treated MDD patients are unable to achieve an adequate response with first-line therapy, and most of these initial failures also fail second-line treatment, according to results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, the largest prospective clinical trial of MDD treatments, published in 2010. In the major markets of the United States, Europe and Japan there are estimated to be more than 13 million MDD patients who have failed one prior class of antidepressant therapy, and an estimated 3.4 million who have failed two prior classes of antidepressants.

Even for patients deemed responsive, disease burden often persists through the presence of residual depression symptoms that lead to an ongoing negative impact on home life and interpersonal functioning, as well as a significantly increased risk of relapse of the full depressive syndrome and worse comorbid outcomes, including suicide. All the currently available classes of treatment have side effects that can negatively impact treatment outcomes, quality of life and adherence to medication, including weight gain, nausea, sexual dysfunction, fatigue, insomnia and numerous other adverse effects. In addition, typically current therapeutic treatments take up to six weeks before efficacy is established, which exposes patients to additional potential side effects and an increased period of suffering, before it is established if a treatment is working. In part because of the long time to achieve benefit from current antidepressant therapies, many people with MDD opt to stay on their treatment chronically, enduring longer periods of side effects, rather than opting for episodic treatment.

Because MDD is increasingly acknowledged as a fluid spectrum of mood disorders and the patient population is heterogeneous, polypharmacy and treatment-switching strategies that consider a patient's dynamic course of disease and fluctuating symptoms are becoming more commonplace. There is a need both for novel treatments with alternative mechanisms of action as well as treatments that improve upon liabilities of existing drugs. Importantly, because of patient heterogeneity, switching therapies within a class can lead to improvements in efficacy and tolerability which can be as impactful as switching to a medication in a different class.

Perimenopausal Depression (PMD)

PMD describes the development of depressive symptoms and major depressive episodes in women during the approximately four-to-eight-year period of menopausal transition occurring in women between approximately 45-55 years of age, with an estimated 50 million women worldwide reaching menopause annually.

The perimenopausal period is associated with multiple neurologic symptoms believed to be associated with a reduction of estrogen/progesterone production and consequently a disruption of multiple estrogen/progesterone-regulated systems in neuronal circuits.

Various studies have found the prevalence of depression symptoms in women during this perimenopausal period as between 15% and 50%. While women with a prior history of MDD are approximately 2-3 times as likely to experience depressive episodes during the perimenopausal period, this period is associated with a 2-fold increased risk in the development of significant depression symptoms in women with no prior history of MDD.

Proven therapies for MDD are recommended as frontline therapy for perimenopausal major depressive episodes, and there is some evidence that estrogen therapy in perimenopausal patients may have antidepressant effects, though it is not approved to treat perimenopausal depression. As with MDD, currently available anti-depressant/anti-psychotic therapies do not provide the desired efficacy in the majority of perimenopausal women, and these agents continue to have the same tolerability liabilities. Novel treatments, which are safe, well-tolerated and rapidly acting are needed. Antidepressant therapies that can also address other symptoms of perimenopause such as hot flashes, insomnia, pain and decline in cognitive function, all of which may contribute to the development of depressive symptoms, are needed.

The opportunity for $GABA_A$ PAMs in the treatment of hormone-related depression has been validated by the clinical success of brexanolone and SAGE-217 in women with PPD, which, like PMD, is also linked to dramatic fluctuations in estrogen/progesterone levels. Brexanolone received FDA approval for the treatment of PPD in 2019 after demonstrating statistically significant and clinically meaningful reductions in the Hamilton Rating Scale for Depression (HAM-D) score with a 60-hour IV infusion of brexanolone compared to placebo in Phase 3 trials. Similarly, the orally administered $GABA_A$ PAM, SAGE-217, demonstrated statistically significant reductions in HAM-D in a Phase 3 trial in women with PPD.

MDD and PMD Unmet Need and Opportunity for ETX-155

Despite numerous antidepressant treatment options, there continues to be an unmet need for antidepressants that provide rapid onset of effect, higher remission rates, efficacy throughout the depressive episode, an improved tolerability profile and an episodic dosing schedule that is aligned with the episodic nature of the disease. A $GABA_A$ PAM that potentiates the activity of endogenous neuroactive steroids at $GABA_A$ receptors may offer broader and more rapid therapeutic benefit compared to current standard of care antidepressants, potentially enabling effective episodic treatment of depressive episodes as they arise. Further, we believe a $GABA_A$ PAM like ETX-155 with the potential differentiated ability to be dosed once a day in the evening with no clinically meaningful food effect could create an exciting commercial opportunity in an attractive, expanding market.

Epilepsy and Focal Onset Seizure

Epilepsy is a chronic CNS condition characterized by recurring seizures arising from hyperexcitable neuronal circuits. The condition encompasses multiple seizure types and syndromes, diverse etiologies and variable prognoses and as such, classification systems have been developed. Classification is made at three levels: seizure type, epilepsy type and syndrome. At each stage, cause and comorbidities should be identified as these can have important therapeutic implications. Most seizures can be categorized as either “focal” or “generalized”, depending on whether the onset of electrical activity affects one side (focal) or both sides (generalized) of the brain.

Epilepsy is the most prevalent chronic brain disease and affects an estimated 50 million people worldwide with over 4.7 million cases in the major markets of the United States, Europe and Japan. FOS (also referred to as focal seizure, partial-onset seizure, or localization-related epilepsy) is a category of seizures that originate from a localized region of the brain and represent the most common seizure disorder encountered in patients with epilepsy. According to the National Institute of Neurological Disorders and Stroke, about 60% of people with epilepsy experience FOS/partial-onset seizures.

The aim of ASM therapy is to achieve a seizure-free status without debilitating adverse side effects. Current standard of care for epilepsy/FOS is treatment with one or more ASMs in continuous prophylactic schemes. There are approximately 30 ASMs currently approved in the United States, which act via several different mechanisms including sodium/calcium channel inhibition, potassium channel activation and glutamate receptor antagonism, among others. Many approved ASMs have Black Box warnings and/or dose-limiting side effects that can limit the ability to maintain therapeutic dose levels necessary for seizure control, with adverse effects including sedation, ataxia, cognitive impairment, weight gain and agitation. Because of the diversity of mechanisms, polypharmacy of ASMs is common if patients fail first-line therapy or have tolerability issues, with the addition of new drugs to a regimen, or switching to alternative drugs, to provide better seizure control and/or improved tolerability.

Despite the range of treatment options available, approximately one-third of epilepsy patients with focal onset seizures are considered drug-resistant and are either unable to maintain seizure control after three prior ASM therapies, or are unable to tolerate such ASMs. The inability to control seizures may result in severe disability, increased mortality rates and socioeconomic consequences such as lower levels of employment and income and increased direct and indirect healthcare costs. Although seizures are the most striking clinical manifestation of epilepsy, other effects on quality of life arise from common co-morbidities including cognitive dysfunction (*e.g.*, memory, attention, or processing difficulties), sleep disorders, migraines and mental health/mood disorders (*e.g.*, depression and anxiety).

Depression is the most common co-morbidity of epilepsy, with a reported lifetime prevalence of major depression in approximately 30% among individuals with epilepsy. This increased rate of depression may in part be due to the side effects of current ASMs, a comorbidity of epilepsy itself, or a combination of the two.

Focal Onset Seizure Opportunity for ETX-155

By acting as a positive allosteric modulator of $GABA_A$Rs, ETX-155 is designed to increase the effect of the inhibitory neurotransmitter GABA, potentially leading to anticonvulsant activity. As a result of its preclinical anti-convulsant activity and its potential positive impact on mood, we believe that ETX-155 has the potential to be positioned as a differentiated treatment option in refractory focal onset seizure. A well-tolerated, novel ASM with a favorable efficacy profile in refractory focal onset seizures combined with a positive impact on mood would be a clinically differentiated profile and an attractive alternative for patients.

ETX-155 Preclinical Development

ETX-155: a potent positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors

ETX-155 is designed as a neurosteroid $GABA_A$R positive allosteric modulator and has dual potency at both synaptic and extrasynaptic receptors. Using automated patch clamp electrophysiology against 19 different synaptic and extrasynaptic $GABA_A$ receptor subtypes, ETX-155 demonstrated approximately equal potency on all subtypes, with EC50 values ranging from 95 nM to 330 nM including 207 nM and 165 nM EC50 at the most predominant synaptic (α1ß2g2) and extrasynaptic (α4ß3g) subtypes, respectively.

High intrinsic activity, a measure of the potentiation of $GABA_A$ currents, was demonstrated across $GABA_A$ receptor subtypes, with ETX-155 having an approximately 3 times higher intrinsic activity at extrasynaptic α4ß3g subtype (1530%) vs. synaptic α1ß2g2 (586%).

In our in vitro assessments, the potency and activity of ETX-155 across $GABA_A$ subtypes was comparable to that of SAGE-217 and ganaxolone. In contrast, data publicly disclosed by Praxis Precision Medicines reported a preference for extrasynaptic versus synaptic $GABA_A$ receptors for the neurosteroid $GABA_A$ PAM, PRAX-114.

Preclinical anti-seizure activity

We investigated the preclinical activity of ETX-155 in a pentylenetetrazol (PTZ) induced seizure model and a maximal electroshock (MES) model of epilepsy, which are well-established predictive models for clinical anti-convulsant activity. In these studies, ETX-155's activity was evaluated in parallel experiments with ganaxolone, another $GABA_A$ PAM in development for epilepsy indications, and valproate was used as a positive control. In both the PTZ and MES models, ETX-155 and valproate demonstrated encouraging dose-dependent anticonvulsant activity. The $GABA_A$ PAM ganaxolone did not achieve statistically significant efficacy in either model at matched doses up to 10 mg/kg.

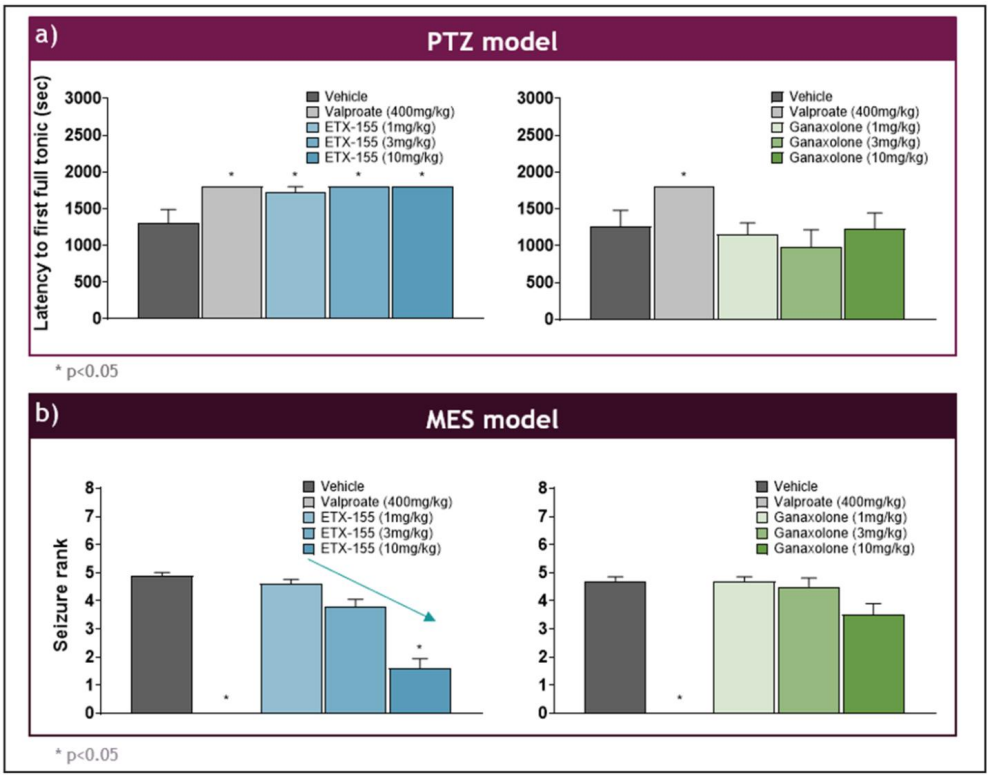

Figure 14. Activity of ETX-155, ganaxolone and valproate (positive control) in two preclinical seizure models. (a) Mice were pretreated with control or test article and then were given a bolus intraperitoneal injection of PTZ to induce acute seizures, followed by the observation of the seizure profile and latency times. ETX-155 (at all doses tested) and valproate significantly increased the latency time to the first full tonic seizure. Ganaxolone did not achieve statistical significance in this experiment. (b) The MES model is an electrically-induced acute seizure model of generalized tonic-clonic seizures. Mice were pretreated with control or test article and then were subjected to seizure-inducing electric shock. The magnitude of the resulting seizure was evaluated using a seizure severity ranking from 0 to 6. Valproate and 10 mg/kg of ETX-155 significantly decreased the seizure rank. Ganaxolone did not achieve statistical significance in this experiment.

Preclinical anti-depressant and anxiolytic activity

The activity of ETX-155 was investigated in preclinical models of anxiety and depression. The anxiety models included the elevated plus maze, social interaction and marble burying paradigms. ETX-155 and SAGE-217, another $GABA_A$ PAM in development for mood disorder indications, showed a dose-dependent efficacy in all models. As shown in *Figure 15a* a, ETX-155 and SAGE-217 dose-dependently improved the time spent in open arms (a measure hypothesized to reflect reduced levels of anxiety) in the rat elevated plus maze behavioral model. The forced swim model in rats was used to assess to potential anti-depressant activity of ETX-155 and SAGE-217 (*Figure 15b*). Both compounds demonstrated a dose-dependent statistically significant efficacy.

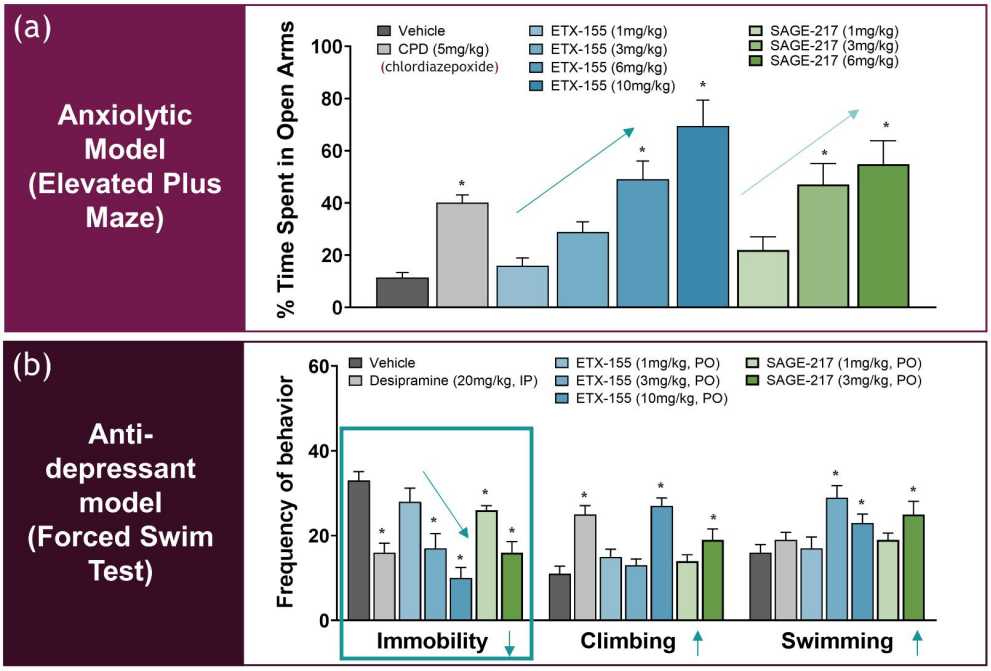

Figure 15. Efficacy of ETX-155 and SAGE-217 in (a) an anxiolytic (elevated plus maze) preclinical model in rats, where the anxiety level is evaluated by the amount of time animals spent in the open arms of a plus-shaped apparatus with two open and two enclosed arms. (b) a depression (forced swim test) model in rats based on the animal's level of activity (climbing or swimming) when placed in an enclosed container filled with water, where the level of immobility of the animal is hypothesized to indicate a depressive mood.

Preclinical EEG model as a biomarker of dose-dependent target engagement

We used electroencephalography (EEG) to investigate the effect of ETX-155 on brain activity in rats. In this model, changes in the EEG spectral power, reflecting a change in cortical neuronal activity, serve as a robust pharmacodynamic biomarker for target engagement with strong translatability from rats to humans. ETX-155 increased spectral power of the theta, alpha, beta, and low gamma frequencies, and decreased the power of the high gamma frequency. Figure 16 below demonstrates the dose-dependent increase in beta power during wake and non-rapid eye movement (NREM) sleep.

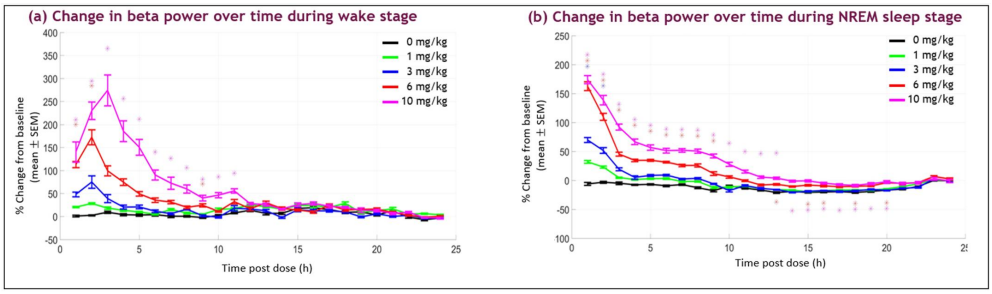

Figure 16. Effect of ETX-155 (1, 3, 6, or 10 mg/kg) on sleep and cortical activity in rats (n=12, cross-over study design). (a) change in beta spectral power over time during wake stage (b) change in beta spectral power over time during NREM sleep. Animals were dosed at 8pm and EEGs were recorded from 2 hours pre-dose to 22 hours post-dose.

Clinical Development

ETX-155 Repeat Dose Phase 1 trials

The 7-day repeat dose portion of our Phase 1 trial of ETX-155 (Study 020155-101) enrolled two cohorts of subjects, with 12 participants in each cohort dosed for 7 days. The first cohort was dosed with 60 mg of ETX-155 daily in the morning while fasted while the second cohort was dosed 60 mg of ETX-155 daily in the evening at approximately 8:00 PM. Both cohorts consisted of nine active subjects and three placebo subjects. In both cohorts, no significant adverse events were seen, there were no subject discontinuations nor were there any clinically significant abnormal values in vital signs, ECGs and clinical labs. However, the 60 mg cohort dosed in the evening experienced fewer adverse events. The advantage of dosing $GABA_A$ PAMs in the evening has also been demonstrated with other molecules in clinical development such as SAGE-217, PRAX-114 and ganaxolone.

In the 7-day repeat dose Phase 1 trial, ETX-155 was well tolerated with no dose limiting AEs, no discontinuations and no abnormal clinical values. We believe the safety and tolerability data observed in this trial compare favorably to other $GABA_A$ PAMs in clinical development. With respect to pharmacokinetics, during this portion of the trial, ETX-155 did not reach steady-state drug levels at day seven and moderate accumulation was seen. Pharmacokinetic modeling suggested that steady-state was likely to be reached shortly after day seven. Therefore, we initiated an additional randomized, placebo-controlled 14-day repeat-dose trial in healthy human subjects to evaluate the pharmacokinetic parameters at steady-state and generate additional data on the tolerability and safety profile of ETX-155.

The 14-day repeat dose Phase 1 clinical trial (Study 020155-102) was completed in the fourth quarter of 2021. This study evaluated the pharmacokinetic profile and safety of ETX-155 in 20 healthy human subjects, evaluating 60 mg ETX-155 (n=15) or placebo (n=5) dosed daily in the evening for 14 days. The results demonstrated that ETX-155 reached steady state concentrations in plasma by the eighth day of dosing and had an approximate 40-hour half-life, confirming ETX-155's desirable profile for a once-daily dosing regimen. The study also confirmed that ETX-155 was generally well tolerated with no severe or serious adverse events, or discontinuations. All treatment emergent adverse events (TEAEs), including CNS adverse events, were mild/moderate and transient. In particular, all somnolence adverse events were mild and the incidence was comparable in the ETX-155 and placebo groups. Notably, somnolence events were sporadic, and no subject who reported somnolence in either the ETX-155 or placebo arms reported it more than one time during the dosing or follow-up period. In addition, there was no clinically meaningful difference compared to placebo in sleep quality or next morning state of arousal, as measured by the Leeds Sleep Evaluation Questionnaire. The tolerability and safety findings of this study were consistent with those of the previous 7-day repeat dose Phase 1 study.

Figure 17 below summarizes the adverse events observed of ETX-155's repeat dose Phase 1 trials in healthy human subjects.

Most common treatment-emergent AEs
(In ≥10% of ETX-155 treated subjects across repeat dose studies)

	7-day Repeat Dose		14-day Repeat Dose		Combined	
	ETX-155 60 mg (n=9)	Placebo (n=6)	ETX-155 60 mg (n=15)	Placebo (n=5)	ETX-155 60 mg (n=24)	Placebo (n=11)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≥1 TEAE	**5 (56)**	3 (50)	**9 (60)**	4 (80)	**14 (58)**	7 (64)
Somnolence	**1 (11)**	2 (33)	**6 (40)**	2 (40)	**7 (29)**	4 (36)
Fatigue	**0**	0	**4 (27)**	1 (20)	**4 (17)**	1 (9)
Headache	**2 (22)**	2 (33)	**1 (7)**	0	**3 (13)**	2 (18)
Dizziness	**1 (11)**	0	**2 (13)**	0	**3 (13)**	0

Figure 17. Summary of all treatment emergent adverse events from the evening dose cohorts of the repeat dose Phase 1 trials in healthy human subjects, evaluating 60 mg ETX-155 dosed daily in the evening for either 7 days or 14 days.

Our analysis of the plasma concentrations observed for the 60 mg dose of ETX-155 in the 7-day repeat dose trial found that the mean plasma exposure at day 7 was consistent with the range of exposures where robust activity was observed in our depression, anxiety, anticonvulsant and EEG preclinical models. In addition, the exposures achieved with the 60 mg dose of ETX-155 in the MAD in healthy volunteers are consistent with those modeled for another $GABA_A$ PAM, zuranolone (SAGE-217), at the 30 mg and 50 mg dose levels in its MAD trial in healthy volunteers. This observation increases our confidence that the 60 mg dose achieves the necessary level of exposure to potentially be an efficacious dose in the indications we are pursuing. Combined with the favorable tolerability data demonstrated by this dose level in the Phase 1 trials, we intend to move forward with this dose into our future clinical trials in patients.

As part of the 14-day repeat dose trial we also conducted exploratory metabolite identification from plasma and urine PK samples. Metabolites were identified, and additional metabolite characterization and qualification work is ongoing.

ETX-155 Phase 1b Photosensitive Epilepsy trial

We initiated a double-blind crossover Phase 1b trial in Photosensitive Epilepsy (PSE) patients in November 2021 with interim data expected in the first half of 2022. Pharmacological effects in PSE proof-of-concept trials are correlated with a higher likelihood that anticonvulsant effect will be observed in later stage epilepsy studies. Assuming the results of this trial are positive, we plan to initiate a Phase 2 clinical trial in patients with focal onset seizures in the first half of 2023.

Planned Phase 2 clinical trials for ETX-155 in depression

We plan to initiate two randomized, placebo-controlled Phase 2a proof-of-concept trials of ETX-155 in MDD and PMD, respectively, in the first half of 2022, assuming FDA clearance of our IND filed with the psychiatry division in the first quarter of 2022.

ETX-155 Phase 2a in MDD

This is a Phase 2a, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 28-day study to evaluate the safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics of ETX-155 in male and female subjects aged 18 to 70 years with recurrent MDD that has previously responded to treatment. The study will enroll subjects who have a current diagnosis of MDD for at least 4 weeks before screening. The study will include a screening phase, a 28-day treatment phase, and a post-treatment follow-up phase. A total of 80 subjects are planned to be randomized in a 1:1 ratio to the ETX-155 or placebo treatment group.

ETX-155 Phase 2a in PMD

This is a Phase 2a, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 28-day study to evaluate the safety, tolerability, efficacy, PK, and PD of ETX-155 in perimenopausal or menopausal women aged 40 to 67 years who have a current diagnosis of MDD that has been present for at least 4 weeks before screening. The study will include a screening phase, a 28-day treatment phase, and a post-treatment follow-up phase. A total of 80 subjects are planned to be randomized in a 1:1 ratio to the ETX-155 or placebo treatment group.

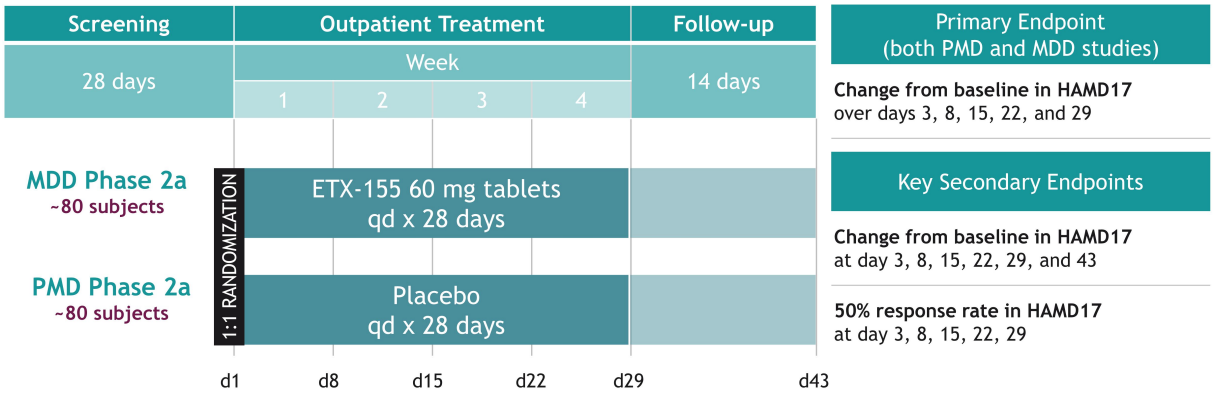

Figure 18. ETX-155 MDD and PMD Phase 2a study design

The primary endpoint for both MDD and PMD Phase 2a trials is the change from baseline over days 3, 8, 15, 22, and 29 in the 17-item Hamilton Rating Scale for Depression (HAMD-17) total score. Topline data from both studies is expected in the second half of 2023.

Preclinical Pipeline

Kv7.2/3 Program for Epilepsy and Pain

Our lead preclinical program is a next-generation Kv7.2/3 channel opener being developed for potential use in epilepsy, neuropathic pain, and depression. Kv7.2/3 is a heteromeric voltage-gated potassium channel comprised of Kv7.2 and Kv7.3 subunits (Kv7.2/3) that plays an important role in stabilizing the membrane potential of neuronal cells and controlling neuronal excitability. Kv7.2/3 has genetic validation as a target for epilepsy, as loss-of-function mutations in the genes encoding for Kv7.2 and Kv7.3, KCNQ2 and KCNQ3, have been shown to be responsible for a rare epilepsy disorder in newborns that leads to impaired gating of the Kv7.2/3 channel and hyperexcitation of neurons.

In addition to its genetic validation, Kv7.2/3 has been clinically validated as a therapeutic target for both epilepsy and pain. The first generation Kv7 channel opener, ezogabine (Potiga), was approved for refractory focal onset seizures in 2011 in both the United States and in Europe (where it was known as retigabine, or Trobalt). Flupirtine (Katadolon) was another first generation Kv7.2/3 opener that provided clinical validation and has been used in Europe as a treatment for pain since the 1980s. Despite demonstrating compelling efficacy in epilepsy and pain, ezogabine/retigabine and flupirtine were removed from the market in 2017 and 2018, respectively, due to emergent unexpected safety concerns. In the case of ezogabine, an accumulation of blue pigment in the skin and eye was identified, raising concerns of potential vision loss, while flupirtine was associated with severe liver toxicity, including cases of acute liver failure. Xenon Pharmaceuticals' Kv7 targeted agent, XEN1101, also reported positive data in a Phase 2b study in focal onset seizure in October 2021, providing further clinical validation for this mechanism.

We have used a combination of both ligand-based and structure-based design approaches to develop novel Kv7.2/3 opener compounds that potentially eliminate the toxicity liabilities associated with the first generation Kv7.2/3 openers, while retaining strong activity and selectivity. We plan to initiate IND-enabling studies for this program in 2022.

Next-generation Anxiolytic for Generalized Anxiety Disorder (GAD)

Our second preclinical program is focused on developing a novel, potent analog of an earlier approved 2,3-benzodiazepine for the potential treatment of GAD. The aim of our program is to develop a rapidly acting, non-sedating, non-addictive anxiolytic that does not impair motor or cognitive performance, does not have any adverse drug-drug interactions, and has the potential to be dosed once a day. We plan to progress preclinical development of this program in 2022.

Competition

The biotechnology industry is characterized by rapid technological advancement, significant competition and an emphasis on intellectual property. We face potential competition from many different sources, including major and specialty pharmaceutical, biopharmaceutical, therapeutics and biotechnology companies, academic research institutions, governmental agencies and public and private research institutions. Any product candidates that we successfully develop and commercialize will compete with current therapies and new therapies that may become available in the future. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective or more convenient or have fewer or less severe side effects than any products that we may develop. Our competitors also may obtain FDA, EMA or other regulatory approval for their products more rapidly than we do. We believe that the key competitive factors affecting the success of any of our product candidates will include efficacy, safety profile, convenience, cost, the level of branded and generic competition, market access and reimbursement by payors, level of promotional activity devoted to them and intellectual property protection.

DPNP and LSRP

In the fields of DPNP and LSRP, our principal competition is from existing therapies including NSAIDs, gabapentinoids, antidepressants, and opioids. Specifically, patients diagnosed with LSRP are usually prescribed with NSAIDs, gabapentinoids (*e.g.*, pregabalin, gabapentin), or opioids. DPNP patients are often treated with antidepressants (*e.g.*, duloxetine, venlafaxine, amitriptyline and other tricyclic drugs), gabapentinoids, or opioids (*e.g.*, tapentadol HCl). We are aware of a number of therapies that are approved to treat other types of neuropathic pain. We are also aware that various therapies are used off-label to treat neuropathic pain. Our competition may also include other programs in clinical development targeting other mechanisms of actions for the treatment of DPNP and LSRP.

Depression and Epilepsy

In the field of neuroactive steroids focused on modulation of $GABA_A$ receptors, our principal competitors are Sage Therapeutics, Inc. developing zuranolone for PPD and MDD, Marinus Pharmaceuticals, Inc. developing ganaxolone for rare epilepsies, and Praxis Precision Medicines, Inc. developing PRAX-114 in MDD. Cerevel Therapeutics, Inc. is also developing a $GABA_A$ PAM, CVL-865, for the treatment of epilepsy, but unlike the neurosteroids, CVL-865 reportedly binds to the benzodiazepine site of synaptic α2/3/5 $GABA_AR$ subtypes.

For the treatment of depressive disorders, we may also face competition from other programs in clinical development targeting other mechanisms of action and approved therapies for depressive disorders such as mixed serotonin modulators, SNRIs, SSRIs, dopaminergic/noradrenergic agents, and atypical antipsychotics. Several biopharmaceutical companies have therapies in clinical development for depressive disorders targeting other mechanisms of action, including Janssen Pharmaceuticals, Axsome Therapeutics and Compass Pathways.

For the treatment of epilepsy, we may also face competition from a variety of currently marketed therapies such as generic anticonvulsants, sodium channel modulators and benzodiazepines. Additionally, there are next-generation therapies in development harnessing the previously mentioned mechanisms of action, such as XEN901 being co-developed by Xenon Pharmaceuticals and Neurocrine Biosciences. Furthermore, there are multiple compounds that have been recently approved or are in late-stage development for focal onset seizures, including cenobamate, which was developed by SK Life Sciences and was approved by the FDA in November 2019, and XEN1101, being developed by Xenon Pharmaceuticals.

We expect to face competition from existing products and products in development for each of our product candidates. In addition to those described above, there may be other earlier stage clinical programs that, if approved, would compete with our product candidates. Many of our competitors have substantially greater financial, technical, manufacturing, marketing, sales and supply resources or experience than we do. Additional mergers and acquisitions in the pharmaceutical industry may result in even more resources being concentrated in our competitors. Competition may increase further as a result of advances made in the commercial applicability of technologies and greater availability of capital for investment in these fields. Our success will be based in part on our ability to build and actively manage a portfolio of drugs that addresses unmet medical needs and creates value in patient therapy.

Intellectual Property

Our commercial success will depend in part on our ability to obtain and maintain proprietary protection for our product candidates and any associated novel discoveries, drug development technologies and know-how; to operate without infringing on or otherwise violating the proprietary rights of others; and to prevent others from infringing or otherwise violating our proprietary rights. Our policy is to seek to protect our proprietary position for our product candidates by, among other methods, filing and acquiring U.S. and foreign patents and patent applications related to our products and other proprietary technology, inventions and improvements that are important to the development and implementation of our business. We also rely on trade secrets, know-how, continuing technological innovation and potential in-licensing opportunities to develop and maintain our proprietary position.

Our intellectual property estate is designed to provide multiple layers of protection, including: (1) patents and patent applications with claims directed to our product candidates; (2) patent applications with claims directed to methods of treatment using our product candidates; and (3) patent applications with claims directed to innovative formulations.

While we seek to cover our product candidates and their use in our issued patents and pending patent applications, there is always a risk that a modification of the product or its use may allow a competitor to avoid infringement claims. In addition, patents, if granted, expire, and we cannot provide any assurance that any patents will be issued from our pending or any future applications or that any issued patents will adequately protect our products.

ETX-810. The compound in this product candidate is covered by a patent family that covers the compound (both generically and specifically) and use of the compound to treat various pain conditions. This patent family includes an issued U.S. patent and pending patent applications in the United States, Australia, Canada, China, Europe, Hong Kong and Japan. The European Patent Office recently confirmed that the European patent application will be considered allowable subject to minor modifications. The compound portfolio is expected to expire on October 12, 2037, excluding any patent term extension or adjustments that may be granted. We also filed a priority application in the United Kingdom covering a new process for preparing ETX-810 and a US provisional application covering a new formulation comprising ETX-810.

We will leverage new discoveries we are making in the research of ETX-810 by filing patent applications thereon to strengthen the breadth and depth of our patent coverage for this product candidate.

ETX-155. Our intellectual property portfolio covering ETX-155 includes two issued U.S. patents, a first with method claims covering use of the composition of matter to treat an anxiety disorder, depression, or a seizure disorder; and a second with composition claims covering a controlled release formulation of ETX-155. The portfolio additionally includes two pending international patent applications under the Paris Cooperation Treaty (PCT) that preserve our future right to file these PCT international applications into individual foreign countries and a pending U.S. application with method claims covering uses of the composition of matter to treat sleep disorders. The issued U.S. patents and any future patents claiming priority thereto are expected to expire in September 2039, excluding any patent term extensions or adjustments that may be granted. Any foreign patents that issue claiming priority to the international application are expected to expire in September 2040. In the last year, we also filed multiple U.S. provisional applications covering methods of treatment and formulations of ETX-155.

We are also working to develop new formulations of ETX-155 and new uses for ETX-155, which we intend to file patent applications on in order to expand the layers of protection provided by our intellectual property estate.

Patent Protection and Terms

Individual patents extend for varying periods depending on the date of filing of the patent application or the date of patent issuance and the legal term of patents in the countries in which they are obtained. Generally, patents issued from regularly filed applications in the United States are granted a term of 20 years from the earliest effective filing date. In addition, in certain instances, a patent term can be adjusted to recapture a portion of the United States Patent and Trademark Office (USPTO), delay in issuing the patent, and extended to recapture a portion of the patent term effectively lost as a result of the FDA regulatory review period of the drug covered by the patent. However, as to the FDA component, the restoration period cannot be longer than five years, the total patent term including the restoration period must not exceed 14 years following FDA approval of the drug, and the extension may only apply to one patent that covers the approved drug (and to only those patent claims covering the approved drug, a method for using it, or a method for manufacturing it). There can be no assurance that any such patent term adjustment or extension will be obtained. The duration of foreign patents varies in accordance with provisions of applicable local law, but typically is also 20 years from the earliest effective filing date. However, the actual protection afforded by a patent varies on a product-by-product basis, from country to country, and depends upon many factors, including the type of patent, the scope of its coverage, the availability of regulatory-related extensions, the availability of legal remedies in a particular country and the validity and enforceability of the patent.

Furthermore, the patent positions of biotechnology and pharmaceutical products and processes like those we intend to develop and commercialize are generally uncertain and involve complex legal and factual questions. No consistent policy regarding the breadth of claims allowed in such patents has emerged to date in the United States. The patent situation outside the United States is even more uncertain. Changes in either the patent laws or in interpretations of patent laws in the United States and other countries can diminish our ability to protect our inventions and enforce our intellectual property rights, can make it easier to challenge the validity, enforceability or scope of any patents that may issue, and, more generally, could affect the value of our intellectual property. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in our patents or in third-party patents.

Third-Party Patent Filings

Numerous U.S. and foreign issued patents and patent applications owned by third parties exist in the fields in which we are developing products. In addition, because patent applications can take many years to issue, there may be applications unknown to us, which may later result in issued patents that our products or proprietary technologies may infringe. Moreover, we may be aware of patent applications, but incorrectly predict the likelihood of those applications issuing with claims of relevance to us.

Under U.S. law, a person may be able to patent a discovery of a new way to use a previously known compound, even if such compound itself is patented, provided the newly discovered use is novel and non-obvious. Such a method-of-use patent, however, if valid, only protects the use of a claimed compound for the specified methods claimed in the patent. This type of patent does not prevent persons from using the compound for any previously known use of the compound. Further, this type of patent does not prevent persons from making and marketing the compound for an indication that is outside the scope of the patented method.

Trade Secrets and Other Protections

In addition to the protections afforded by patents and other regulatory protections, we may rely, in some circumstances, on trade secrets to protect our technology. Trade secrets may be useful to protect proprietary know-how that is not patentable or which we elect not to patent. Trade secrets may also be useful for processes or improvements for which patents are difficult to enforce. We also protect our products and proprietary technology through confidentiality agreements with employees, consultants, advisors, contractors and collaborators. These agreements are designed to protect our proprietary information and, in the case of the invention assignment agreements, to grant us ownership of technologies that are developed through a relationship with a third party. These agreements may be breached, and we may not have adequate remedies for any such breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our commercial partners, collaborators, employees and consultants use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems.

Infringement of Third-Party Proprietary Rights

Our commercial success will depend in part on not infringing upon or otherwise violating the intellectual property and proprietary rights of third parties. If we are found to infringe a third party's intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our products and technology. 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. We could also be forced, including by court order, to cease commercializing the infringing product or technology. 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 our products or force us to cease some of our business operations. For more information regarding these risks, see the section titled "Risk Factors—Risks Related to Intellectual Property."

Manufacturing

We do not own or operate, and currently have no plans to establish, any manufacturing facilities. We currently source all of our nonclinical and clinical compound supply through third-party contract development and manufacturing organizations (CDMOs).

For clinical supply, we use CDMOs who are obligated to act in accordance with the FDA's current Good Manufacturing Practices (cGMPs), for the manufacture of drug substance and product. We expect to rely on third parties for our manufacturing processes and the production of all clinical supply drug substance and drug product and currently expect to continue to do so for commercial supplies of our product candidates, if approved. We use additional contract manufacturers to fill, label, package, store and distribute our investigational drug products and currently expect to continue to do so for commercial supplies of our product candidates, if approved. It is our intent to identify and qualify additional manufacturers to provide active pharmaceutical ingredient and fill-and-finish services prior to submission of a new drug application (NDA) to the FDA for any product candidates that complete clinical development.

Government Regulation

The FDA and comparable regulatory authorities in state and local jurisdictions and in other countries impose substantial and burdensome requirements upon companies involved in the clinical development, manufacture, marketing and distribution of prescription drugs, such as those we are developing. These agencies and other federal, state and local entities regulate, among other things, the research and development, testing, manufacture, quality control, safety, effectiveness, labeling, storage, record keeping, approval, advertising and promotion, distribution, post-approval monitoring and reporting, sampling and export and import of drug products and product candidates. The process of obtaining regulatory approvals and the subsequent compliance with applicable federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources.

U.S. Government Regulation of Drug Products

In the United States, the FDA regulates drugs under the Federal Food, Drug and Cosmetic Act (FDCA) and its implementing regulations. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant to a variety of administrative or judicial sanctions, such as the FDA's refusal to approve pending NDAs withdrawal of an approval, imposition of a clinical hold, issuance of warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties brought by the FDA and the Department of Justice (DOJ) or other governmental entities.

The process required by the FDA before a drug may be marketed in the United States generally involves the following:

Completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice (GLP) regulations;

- Submission to the FDA of an IND which must become effective before human clinical trials may begin;
- Approval by an independent institutional review board (IRB) at each clinical site before each trial may be initiated;
- Performance of adequate and well-controlled human clinical trials in accordance with good clinical practice (GCP), requirements to establish the safety and efficacy of the proposed drug product for each indication;

- Submission to the FDA of an NDA;
- Satisfactory completion of an FDA advisory committee review, if applicable;
- Satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with cGMP requirements and to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity;
- Satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of the clinical data;
- Payment of user fees and securing FDA approval of the NDA, including agreement to compliance with any post-approval requirements; and
- Compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy (REMS), and the potential requirement to conduct post-approval studies.

Preclinical studies

Before testing any drug or biological product candidate, including our product candidates, in humans, the product candidate must undergo rigorous preclinical testing. Preclinical studies generally include laboratory evaluation of product chemistry, formulation and stability, as well as animal studies to assess potential toxicity, which support subsequent clinical testing. Prior to beginning the first clinical trial with a product candidate in the United States, we must submit an IND to the FDA. An IND is a request for authorization from the FDA to administer an investigational new drug product to humans. The central focus of an IND submission is on the general investigational plan and the protocol(s) for clinical studies. Some preclinical testing may continue even after the IND is submitted. The IND also includes results of animal and in vitro studies assessing the toxicology, pharmacokinetics, pharmacology, and pharmacodynamic characteristics of the product; chemistry, manufacturing, and controls information; and any available human data or literature to support the use of the investigational product. An IND must become effective before human clinical trials may begin. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises safety concerns or questions about the proposed clinical trial. In such a case, the IND may be placed on clinical hold and the IND sponsor and the FDA must resolve any outstanding concerns or questions before the clinical trial can begin. Submission of an IND therefore may or may not result in FDA authorization to begin a clinical trial.

Clinical trials

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

In addition, an IRB at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it initiates at that institution. An IRB is charged with protecting the welfare and rights of trial participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the informed consent form that must be provided to each clinical trial subject or his or her legal representative and must monitor the clinical trial until completed. Regulatory authorities, the IRB or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects are being exposed to an unacceptable health risk or that the trial is unlikely to meet its stated objectives. Some studies also include oversight by an independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board, which provides authorization for whether or not a study may move forward at designated check points based on access to certain data from the study and may halt the clinical trial if it determines that there is an unacceptable safety risk for subjects or other grounds, such as no demonstration of efficacy. There are also requirements governing the reporting of ongoing clinical studies and clinical study results to public registries. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health (NIH) for public dissemination on their www.clinicaltrials.gov website. Information related to the product, patient population, phase of investigation, study sites and investigators and other aspects of the clinical trial is made public as part of the registration of the clinical trial. Sponsors are also obligated to disclose the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed in some cases for up to two years after the date of completion of the trial.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined:

- Phase 1: The drug is initially introduced into healthy human subjects or patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness.
- Phase 2: The drug is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.
- Phase 3: The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product, and to provide adequate information for the labeling of the product. Generally, two adequate and well-controlled Phase 3 clinical trials are required by the FDA for approval of an NDA.

Post-approval trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow up. In certain instances, the FDA may mandate the performance of Phase 4 clinical trials as a condition of approval of an NDA.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. The FDA or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. In addition, some clinical trials are overseen by an independent group of qualified experts organized by the sponsor, known as a data safety monitoring board or committee. Depending on its charter, this group may determine whether a trial may move forward at designated check points based on access to certain data from the trial.

During the development of a new drug, sponsors are given opportunities to meet with the FDA at certain points. These points are generally prior to submission of an IND, at the end of Phase 2, and before an NDA is submitted. Meetings at other times may be requested. These meetings can provide an opportunity for the sponsor to share information about the data gathered to date, for the FDA to provide advice, and for the sponsor to obtain the FDA's feedback on the next phase of development. Sponsors typically use the meetings at the end of the Phase 2 trial to discuss Phase 2 clinical results and present plans for the pivotal Phase 3 clinical trials that they believe will support approval of the new drug.

Concurrent with clinical trials, companies usually complete additional animal studies and also must develop additional information about the chemistry and physical characteristics of the drug or biologic as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product and, among other things, companies must develop methods for testing the identity, strength, quality and purity of the final product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidates do not undergo unacceptable deterioration over their shelf life.

Marketing application submission and FDA review and approval

Assuming successful completion of the required clinical testing, the results of the preclinical and clinical studies, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. Data may come from company-sponsored clinical trials intended to test the safety and effectiveness of a use of a product, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and effectiveness of the investigational drug product to the satisfaction of the FDA. In most cases, the submission of an NDA is subject to a substantial application user fee; a waiver of such fees may be obtained under certain limited circumstances. Under the goals and policies agreed to by the FDA under the Prescription Drug User Fee Act (PDUFA), the FDA has ten months from the date of "filing" of a standard NDA for a new molecular entity in which to complete its initial review and respond to the applicant, and six months from the filing date for priority applications.

The FDA does not always meet its PDUFA goal dates, and the review process can be extended by FDA requests for additional information or clarification and a sponsor's process to respond to such inquiries. This FDA review typically takes twelve months from the date the NDA is submitted to FDA (for a standard review) because the FDA has approximately two months, or 60 days, after submission to make a "filing" decision on whether to accept an NDA for review.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are sufficiently complete to permit substantive review and informs the sponsor by the 74th day after the FDA's receipt of the submission whether an application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA reviews an NDA to determine, among other things, whether the drug is safe and effective and whether the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product's continued safety, quality and purity.

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

Additionally, the FDA may refer any application to an advisory committee, including applications for novel drug candidates that present difficult questions of safety or efficacy. An advisory committee is a panel of independent experts, including clinicians and other scientific experts, which reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. The FDA also may require submission of a risk evaluation and mitigation strategy, or REMS, plan, if it determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks and to assure the safe use of the drug product. The REMS plan could include medication guides, physician communication plans, assessment plans and/or elements to assure safe use, such as restricted distribution methods, patient registries or other risk minimization tools. The FDA determines the requirement for a REMS, as well as the specific REMS provisions, on a case-by-case basis. If the FDA concludes a REMS plan is needed, the sponsor of the NDA must submit a proposed REMS. The FDA will not approve the NDA without a REMS, if required.

In addition, under the Pediatric Research Equity Act of 2003, as amended and reauthorized (PREA), certain NDAs or supplements to an NDA must contain data that are adequate to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements.

After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue either an approval letter or a complete response letter (CRL). An approval letter authorizes commercial marketing of the drug with specific prescribing information and for specific indications. A CRL indicates that the review cycle of the application is complete, and the application will not be approved in its present form. A CRL generally outlines the deficiencies in the submission and contains a statement of specific conditions that must be met in order to secure final approval of the NDA; it may require additional clinical or preclinical testing and/or other significant and time-consuming requirements related to clinical trials, preclinical studies or manufacturing in order for FDA to reconsider the application. If a CRL is issued, the applicant may choose to either resubmit the NDA, addressing all of the deficiencies identified in the letter, or withdraw the application. If and when those deficiencies have been addressed to the FDA's satisfaction, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in response to an issued CRL in either two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution and use restrictions or other risk management mechanisms under a REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-marketing studies or surveillance programs. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval. In addition, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could impact the timeline for regulatory approval or otherwise impact ongoing development programs.

Fast track, breakthrough therapy and priority review designations

The FDA is authorized to designate certain products for expedited development or review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs include fast-track designation, breakthrough-therapy designation and priority-review designation.

To be eligible for a fast-track designation, the FDA must determine, based on the request of a sponsor, that a product is intended to treat a serious or life-threatening disease or condition and demonstrates the potential to address unmet medical needs for the condition. Fast track designation provides opportunities for more frequent interactions with the FDA review team to expedite development and review of the product. The FDA may also review sections of the NDA for a fast-track product on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the application, the FDA agrees to accept sections of the application and determines that the schedule is acceptable and the sponsor pays any required user fees upon submission of the first section of the application. The sponsor can request the FDA to designate the product for fast-track status any time before receiving NDA approval, but ideally no later than the pre-NDA meeting. Fast track designation may be withdrawn by the sponsor or rescinded by the FDA if the designation is no longer supported by data emerging in the clinical trial process.

In addition, with the enactment of the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012, Congress created a new regulatory program for product candidates designated by FDA as "breakthrough therapies" upon a request made by IND sponsors. A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over currently approved therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. If the FDA designates a breakthrough therapy, it may take actions appropriate to expedite the development and review of the application, which may include holding meetings with the sponsor and the review team throughout the development of the therapy; providing timely advice to, and interactive communication with, the sponsor regarding the development of the drug to ensure that the development program to gather the nonclinical and clinical data necessary for approval is as efficient as practicable; involving senior managers and experienced review staff, as appropriate, in a collaborative, cross-disciplinary review; assigning a cross-disciplinary project lead for the FDA review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the review team and the sponsor; and considering alternative clinical trial designs when scientifically appropriate, which may result in smaller trials or more efficient trials that require less time to complete and may minimize the number of patients exposed to a potentially less efficacious treatment. Breakthrough therapy designation comes with all of the benefits of fast-track designation, which means that the sponsor may file sections of the NDA for review on a rolling basis if certain conditions are satisfied, including an agreement with the FDA on the proposed schedule for submission of portions of the application and the payment of applicable user fees before the FDA may initiate a review. Finally, the FDA may designate a product for priority review if it is a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines at the time that the marketing application is submitted, on a case-by-case basis, whether the proposed drug represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting drug reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, or evidence of safety and effectiveness in a new subpopulation. A priority review designation is intended to direct overall attention and resources to the evaluation of such applications and to shorten the FDA's goal for taking action on a marketing application from ten months to six months for an NDA for a new molecular entity from the date of filing. If criteria are not met for priority review, the application for a new molecular entity is subject to the standard FDA review period of ten months after FDA accepts the application for filing. Priority review designation does not change the scientific/medical standard for approval or the quality of evidence necessary to support approval.

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

U.S. marketing and data exclusivity

Market exclusivity provisions under the FDCA can delay the submission or the approval of certain follow-on drug applications. The FDCA provides a five-year period of non-patent marketing exclusivity within the United States to the first applicant to gain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an Abbreviated New Drug Application (ANDA) or a 505(b)(2) NDA submitted by another company for a generic or follow-on version of the protected drug product, respectively, where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement.

The FDCA also provides three years of data exclusivity when an NDA or a supplement to an existing NDA, includes new clinical investigations, other than bioavailability studies, conducted or sponsored by the applicant that are deemed by the FDA to be essential to the approval of the application, for example, new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the conditions of use associated with the new clinical investigations and does not prohibit the FDA from approving ANDAs or follow-on 505(b)(2) NDAs if the protected clinical data are not referenced. Five-year and three-year exclusivity will not delay the submission or approval of a stand-alone NDA submitted under section 505(b)(1) of the FDCA. However, an applicant submitting a stand-alone NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness, if applicable.

Pediatric exclusivity is another type of regulatory market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing regulatory exclusivity periods. This six-month exclusivity may be granted based on the voluntary completion of a pediatric trial in accordance with an FDA-issued “Written Request” for such a trial. The issuance of a written request does not require the sponsor to undertake the described clinical trials.

Post-approval requirements

Following approval of a new prescription drug product, the manufacturer and the approved drug are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to monitoring and recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs must be promoted by a manufacturer and any third parties acting on behalf of a manufacturer only for the approved indications and in a manner consistent with the approved label for the product. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses and a company that is found to have improperly promoted off-label uses may be subject to significant liability. After approval, most changes to the approved product, such as adding new indications or other labeling claims or changes to the manufacturing processes or facilities, are subject to prior FDA review and approval. There are continuing, annual user fee requirements for any marketed products and the establishments where such products are manufactured, as well as new application fees for supplemental applications with clinical data.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP requirements and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain cGMP compliance.

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

- Restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- Fines, warning letters or other enforcement-related letters or clinical holds on post-approval clinical trials;
- Refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or suspension or revocation of product approvals;
- Product seizure or detention, or refusal to permit the import or export of products;
- consent decrees, corporate integrity agreements, debarment or exclusion from federal healthcare programs;
- Mandated modification of promotional materials and labeling and the issuance of corrective information;
- Issuance of safety alerts, Dear Healthcare Provider letters, press releases and other communications containing warnings or other safety information about the product; or
- Injunctions or the imposition of civil or criminal penalties.

The FDA also may require post-marketing testing, known as Phase 4 testing, and surveillance to monitor the effects of an approved product. Discovery of previously unknown problems with a product or the failure to comply with applicable FDA requirements can have negative consequences, including adverse publicity, judicial or administrative enforcement, warning letters from the FDA, mandated corrective advertising or communications with doctors, and civil or criminal penalties, among others. Newly discovered or developed safety or effectiveness data may require changes to a product’s approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act (PDMA) which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution. From time to time, new legislation and regulations may be implemented that could significantly change the statutory provisions governing the approval, manufacturing and marketing of products regulated by the FDA. It is impossible to predict whether further legislative or regulatory changes will be enacted, or FDA regulations, guidance or interpretations changed or what the impact of such changes, if any, may be.

Other healthcare laws and regulations

Healthcare providers, including physicians and third-party payors in the United States and elsewhere will play a primary role in the recommendation and prescription of any drug products for which we obtain marketing approval. Our current and future arrangements with third-party payors, customers, healthcare providers, physicians and others, in connection with the clinical research, sales, marketing and promotion of products, once approved, and related activities, may expose a pharmaceutical manufacturer to broadly applicable fraud and abuse and other healthcare laws and regulations. In particular, the research of our product candidates, as well as the promotion, sales and marketing of healthcare items and services and certain business arrangements in the healthcare industry, are subject to extensive laws designed to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, structuring and commission(s), certain customer incentive programs and other business or financial arrangements. The applicable federal, state and foreign healthcare laws and regulations that may affect our ability to operate include, but are not limited to:

- the U.S. federal Anti-Kickback Statute, which makes it illegal for any person or entity, including a prescription drug manufacturer (or a party acting on its behalf), to knowingly and willfully solicit, receive, offer or pay any remuneration (including any kickback, bribe, or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual, or the purchase, lease, order, arrangement, or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. The term remuneration has been interpreted broadly to include anything of value. Further, courts have found that if "one purpose" of renumeration is to induce referrals, the federal Anti-Kickback statute is violated. Violations are subject to significant civil and criminal fines and penalties for each violation, plus up to three times the remuneration involved, imprisonment and exclusion from government healthcare programs. The Anti-Kickback Statute has been interpreted to apply to arrangements between biopharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers, among others, on the other. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution;
- the U.S. federal civil and criminal false claims laws, including the False Claims Act (FCA), which can be enforced through "qui tam" or "whistleblower" actions, and civil monetary penalty laws, which impose criminal and civil penalties against individuals or entities for, among other things, knowingly presenting, or causing to be presented, claims for payment or approval from Medicare, Medicaid, or other federal health care programs that are false, fictitious or fraudulent; knowingly making, using, or causing to be made or used, a false record or statement material to a false, fictitious or fraudulent claim or an obligation to pay or transmit money or property to the federal government; or knowingly concealing or knowingly and improperly avoiding or decreasing or concealing such an obligation. to pay money to the federal government. Manufacturers can be held liable under the FCA even when they do not submit claims directly to government payors if they are deemed to "cause" the submission of false or fraudulent claims. In addition, a claim submitted for payment to any federal healthcare program that includes items or services that were made as a result of a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the FCA. When an entity is determined to have violated the FCA, the government may impose civil fines and penalties for each false claim, plus treble damages, and exclude the entity from participation in Medicare, Medicaid and other federal healthcare programs;
- the U.S. federal Health Insurance Portability and Accountability Act of 1996 (HIPAA), which created additional federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payors, or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (*e.g.*, public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false, fictitious or fraudulent statement or representation, or making or using any false writing or document knowing the same to contain any materially false fictitious or fraudulent statement or entry in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters. Similar to the federal Anti-Kickback Statute, a person or entity can be found guilty of violating HIPAA fraud provisions without actual knowledge of the statute or specific intent to violate it;

- the U.S. federal Physician Payments Sunshine Act and its implementing regulations, which require certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program to report annually to the Centers for Medicare and Medicaid Services (CMS), an agency within the U.S. Department of Health and Human Services (HHS), under the Open Payments Program, information related to direct or indirect payments and other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), other healthcare professionals, (such as physician assistants and nurse practitioners), and teaching hospitals, as well as ownership and investment interests held by the physicians and their immediate family members. Effective January 1, 2022, these reporting obligations will extend to include transfers of value made during the previous year to physician assistants, nurse practitioners, clinical nurse specialists, anesthesiologist assistants, certified registered nurse anesthetists and certified nurse midwives;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and their implementing regulations, also imposes obligations, including mandatory contractual terms, on "covered entities," including certain healthcare providers, health plans, healthcare clearinghouses, and their respective "business associates" that create, receive, maintain or transmit individually identifiable health information for or on behalf of a covered entity as well as their covered subcontractors, with respect to safeguarding the privacy, security and transmission of individually identifiable health information, as well as analogous state and foreign laws that govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.
- U.S. federal and state consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers; and
- analogous U.S. state, local and foreign laws and regulations, such as U.S. state anti-kickback, false claims and laws that may apply to items or services reimbursed by any third-party payor, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and other relevant compliance guidance promulgated by the federal government that otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to file reports with states regarding pricing and marketing information, such as the tracking and reporting of gifts, compensations and other remuneration and items of value provided to healthcare professionals and entities; state and local laws requiring the registration of pharmaceutical sales representatives.

Because of the breadth of these laws and the narrowness of the statutory exceptions and regulatory safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Efforts to ensure that business arrangements comply with applicable healthcare laws involve substantial costs. It is possible that governmental and enforcement authorities will conclude that our business practices do not comply with current or future statutes, regulations or case law interpreting applicable fraud and abuse or other healthcare laws and regulations. If any such actions are instituted against us and we are not successful in defending ourselves or asserting its rights, those actions could have a significant impact on our business, including the imposition of significant civil, criminal and administrative penalties, damages, disgorgement, imprisonment, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, reporting obligations and oversight if we become subject to integrity and oversight agreements to resolve allegations of non-compliance, contractual damages, reputational harm, diminished profits and future earnings and curtailment of operations, any of which could adversely affect our ability to operate our business and the results of operations. In addition, commercialization of any drug product outside the United States will also likely be subject to foreign equivalents of the healthcare laws mentioned above, among other foreign laws. Further, if any of the physicians or other healthcare providers or entities with whom we expect to do business with are found to be not in compliance with applicable laws, they may be subject to similar penalties.

Data privacy and security laws

Numerous state, federal and foreign laws, including consumer protection laws and regulations, govern the collection, dissemination, use, access to, confidentiality and security of personal information, including health-related information. In the United States, numerous federal and state laws and regulations, including state data breach notification laws, health information privacy laws, including HIPAA, and federal and state consumer protection laws (*e.g.*, Section 5 of the Federal Trade Commission Act) that govern the collection, use, disclosure and protection of health-related and other personal information could apply to our operations or the operations of our partners. For example, the California Consumer Protection Act (CCPA) came into effect on January 1, 2020 and provides data privacy rights for consumers and operational requirements for companies. The CCPA gives California residents expanded rights to access and delete their personal information, opt out of certain personal information sharing and receive detailed information about how their personal information is used. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation. Further, the California Privacy Rights Act (CPRA), was recently voted into law by California residents. The CPRA significantly amends the CCPA, and imposes additional data protection obligations on covered companies doing business in California, including additional consumer rights processes and opt outs for certain uses of sensitive data. It also creates a new California data protection agency specifically tasked to enforce the law, which would likely result in increased regulatory scrutiny of California businesses in the areas of data protection and security. The substantive requirements for businesses subject to the CPRA will go into effect on January 1, 2023, and become enforceable on July 1, 2023.

The collection, use, storage, disclosure, transfer, or other processing of personal data regarding individuals in the EEA, including personal health data, is subject to the European Union (EU) General Data Protection Regulation (GDPR), which became effective in May 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches and taking certain measures when engaging third-party processors. The GDPR imposes strict rules on the transfer of personal data to countries outside the European Economic Area (EEA), including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies and obtain compensation for damages resulting from violations of the GDPR.

Further, the exit of the United Kingdom (U.K.), from the EU, often referred to as Brexit, has created uncertainty with regard to data protection regulation in the U.K. From January 1, 2021, companies have to comply with the GDPR and also the United Kingdom GDPR, or the U.K. GDPR, which, together with the amended U.K. Data Protection Act 2018, retains the GDPR in U.K. national law. The U.K. GDPR mirrors the fines under the GDPR, *i.e.*, fines up to the greater of €20 million (£17.5 million) or 4% of global turnover. The relationship between the U.K. and the EU in relation to certain aspects of data protection law remains unclear, and it is unclear how U.K. data protection laws and regulations will develop in the medium to longer term, and how data transfers to and from the U.K. will be regulated in the long term. These changes will lead to additional costs and increase our overall risk exposure. Currently there is a four to six-month grace period agreed in the EU and United Kingdom Trade and Cooperation Agreement, ending June 30, 2021 at the latest, whilst the parties discuss an adequacy decision. The European Commission published a draft adequacy decision on February 19, 2021. If adopted, the decision will enable data transfers from EU member states to the U.K. for a four-year period, subject to subsequent extensions.

Current and future healthcare reform legislation

The FDA's and other regulatory authorities' policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. For example, in December 2016, the 21st Century Cures Act, or Cures Act, was signed into law. The Cures Act, among other things, is intended to modernize the regulation of drugs and devices and to spur innovation, but its ultimate implementation is uncertain. More recently, in August 2017, the FDA Reauthorization Act was signed into law to reauthorize the FDA's user fee programs and included additional drug and device provisions that build on the Cures Act.

In addition, in both the United States and certain foreign jurisdictions, there have been, and likely will continue to be, a number of legislative and regulatory changes regarding the health care system directed at broadening the availability of healthcare, improving the quality of healthcare and containing or lowering the cost of healthcare. For example, in March 2010 the Patient Protection and Affordable Care Act (ACA) was enacted, which substantially changed the way health care is financed by both governmental and private insurers, and significantly impacted the U.S. pharmaceutical industry. The ACA, among other things, subjected biological products to potential competition by lower-cost biosimilars; expanded the types of entities eligible for the 340B drug discount program; introduced a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected; increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations; established annual fees and taxes on manufacturers of certain branded prescription drugs; and created a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (increased to 70% pursuant to the Bipartisan Budget Act of 2018 (BBA), effective as of January 2019) point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D.

Since its enactment, there have been judicial, administrative, executive and legislative challenges to certain aspects of the ACA. On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court's decision, President Biden issued an executive order that initiated a special enrollment period for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is possible that the ACA will be subject to judicial or Congressional challenges in the future. It is unclear how such challenges and the healthcare reform measures of the Biden administration with impact the ACA and our business.

In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. For example, in August 2011, the Budget Control Act of 2011, among other things, included aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect on April 1, 2013, and, due to subsequent legislative amendments, will remain in effect through 2031, with the exception of a temporary suspension from May 1, 2020 through March 31, 2022, unless additional Congressional action is taken. Under current legislation the actual reduction in Medicare payments will vary from 1% in 2022 to up to 3% in the final fiscal year of this sequester. Additionally, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price, for single source and innovator multiple source drugs, beginning January 1, 2024. On January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Moreover, payment methodologies may be subject to changes in healthcare legislation and regulatory initiatives. For example, CMS may develop new payment and delivery models, such as bundled payment models. There also has been heightened governmental scrutiny in the United States of pharmaceutical pricing practices in light of the rising cost of prescription drugs and biologics. Such scrutiny has resulted in several recent U.S. Congressional inquiries, Presidential executive orders, and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs and reform government program reimbursement methodologies for drugs. For example, in July 2021, the Biden administration released an executive order, "Promoting Competition in the American Economy," with multiple provisions aimed at prescription drugs. In response to Biden's executive order, on September 9, 2021, HHS released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue to advance these principles. In addition, Congress is considering drug pricing as part of other health reform initiatives. It is unclear whether the Biden administration will work to reverse measures that were initiated by the former Trump administration or pursue similar policy initiatives.

At the state level, legislatures in the United States have also increasingly passed legislation and implemented regulations designed to control pharmaceutical 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 healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs.

In the European Union and in other foreign jurisdictions, similar political, economic and regulatory developments may affect our ability to profitably commercialize our products. In addition to continuing pressure on prices and cost containment measures, legislative developments at the European Union or EU member state level may result in significant additional requirements or obstacles that may increase our operating costs.

Legislative and regulatory proposals, and enactment of laws, at the foreign, federal and state levels, directed at containing or lowering the cost of healthcare, will likely continue into the future.

Rest of world regulation

For other countries outside of the European Union and the United States, such as countries in Eastern Europe, Latin America or Asia, the requirements governing product development, the conduct of clinical trials, manufacturing, distribution, marketing approval, advertising and promotion, product licensing, pricing and reimbursement vary from country to country. Additionally, clinical trials must be conducted in accordance with GCP requirements and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

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

Additionally, to the extent that any of our product candidates, once approved, are sold in a foreign country, we may be subject to applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws and implementation of corporate compliance programs and reporting of payments or other transfers of value to healthcare professionals.

Additional laws and regulations governing international operations

If we further expand our operations outside of the United States, we must dedicate additional resources to comply with numerous laws and regulations in each jurisdiction in which we plan to operate. The Foreign Corrupt Practices Act (FCPA) prohibits any U.S. individual or business from paying, offering, 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 United States to comply with certain accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the corporation, 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 by U.S. authorities that enforce the FCPA, including DOJ, to be 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 United States, or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. If we expand our presence outside of the United States, it will require us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing, or selling certain products and product candidates outside of the United States, which could limit our growth potential and increase our development costs.

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.

Coverage, pricing and reimbursement

Significant uncertainty exists as to the coverage, pricing and reimbursement status of any products seeking regulatory approval. Successful commercialization of new drug products depends in part on the extent to which coverage and reimbursement for those drug products will be available from government health administration authorities, private health insurers and other organizations. The availability of coverage and extent of reimbursement depend substantially, both domestically and abroad, on the extent to which the costs of drugs products are paid for by third-party payors, such as government health care programs (*e.g.*, Medicare, Medicaid), health maintenance organizations, managed care providers, pharmacy benefit and similar healthcare management organizations, private health coverage insurers and other third-party payors. These third-party payors decide which medications they will pay for and will establish reimbursement levels.

In the United States, no uniform policy of coverage and reimbursement for drug products exists among third-party payors and coverage and reimbursement levels for drug products can differ significantly from payor to payor. Third-party payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates, but also have their own methods and approval process apart from Medicare determinations. Factors payors consider in determining reimbursement are based on whether the product is:

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

Moreover, the process for determining whether a payor will provide coverage for a product may be separate from the process for setting the reimbursement rate that the payor will pay for the product. One payor's determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for the product. Third-party payors may also limit coverage to specific products on an approved list, or formulary, which might not include all of the FDA-approved products for a particular indication.

Increasing efforts by third-party payors in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for newly approved products and, as a result, they may not cover or provide adequate payment for our product candidates. In order to secure coverage and reimbursement for any product that might be approved for sale, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain FDA or comparable regulatory approvals. Additionally, we may also need to provide discounts to purchasers, private health plans or government healthcare programs. Our product candidates, if approved, may nonetheless not be considered medically necessary or cost-effective. If third-party payors do not consider a product to be cost-effective compared to other available therapies, they may not cover the product after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its products at a profit. We expect to experience pricing pressures from third-party payors in connection with the potential sale of any of our product candidates.

Outside of the United States, the pricing of pharmaceutical products and medical devices is subject to governmental control in many countries. For example, in the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost effectiveness of a particular therapy to currently available therapies or so-called health technology assessments, in order to obtain reimbursement or pricing approval. Other countries may allow companies to fix their own prices for products, but monitor and control product volumes and issue guidance to physicians to limit prescriptions. Efforts to control prices and utilization of pharmaceutical products and medical devices will likely continue as countries attempt to manage healthcare expenditures. Historically, products launched in the European Union do not follow price structures of the United States and generally prices tend to be significantly lower.

Employees and Human Capital

As of December 31, 2021, we had 19 full-time employees and 12 part-time employees. Of our 31 employees, nine have Ph.D. or M.D. degrees and 19 are engaged in research and development activities. None of our employees are represented by labor unions or covered by collective bargaining agreements. We consider our relationship with our employees to be good.

Our human capital resources objectives include meeting hiring goals, deepening our neurology research and development and public company expertise, integrating new employees, and retaining, incentivizing and developing our existing employees. We provide discretionary cash-based performance bonuses and, in addition, may utilize our equity incentive plan to attract, retain and motivate selected employees, consultants and directors through the granting of stock-based compensation awards.

Corporate Information

We were incorporated under the laws of the state of Delaware in October 2018. Our principal mailing address is 23515 NE Novelty Hill Road, Suite B221 #125, Redmond, WA 98503. Our telephone number is (425) 276-2300. Our website is www.eliemtx.com. Our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and all amendments to those reports are available free of charge on our website as soon as reasonably practicable after such material is electronically filed with, or furnished to, the Securities and Exchange Commission.

Item 1A. Risk Factors

You should carefully consider the following risk factors, in addition to the other information contained in this Annual Report on Form 10-K, including the section of this report titled "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our consolidated financial statements and related notes. If any of the events described in the following risk factors and the risks described elsewhere in this report occurs, or if any other risks of which we are not presently aware occurs, our business, operating results and financial condition could be seriously harmed. This Annual Report on Form 10-K also contains forward-looking statements that involve risks and uncertainties. Our actual results could differ materially from those anticipated in the forward-looking statements as a result of factors that are described below and elsewhere in this report.

Risks Related to our Financial Position and Need for Additional Capital

We have incurred significant losses since our inception, anticipate that we will incur substantial losses for the foreseeable future and may never achieve or maintain profitability.

We are a clinical-stage biotechnology company with a limited operating history. Our efforts are focused primarily on developing our product candidates, including our two lead clinical-stage candidates, ETX-810 and ETX-155. Since inception, we have incurred significant operating losses. Our net losses were $20.7 million and $47.5 million for the years ended December 31, 2020 and December 31, 2021, respectively. We had an accumulated deficit of $75.6 million and $28.1 million as of December 31, 2021 and December 31, 2020, respectively. To date, we have not received regulatory approvals for any of our product candidates or generated any revenue from the sale of products, and we do not expect to generate any revenue in the foreseeable future. We expect to continue to incur substantial expenses and operating losses over the next several years as we continue to develop our current and future product candidates. As a result, we expect to continue to incur significant losses for the foreseeable future. We anticipate that our expenses will increase substantially as we:

- continue to develop and conduct clinical trials, including for ETX-810 and ETX-155 for our initial and any potential additional indications;
- initiate and continue research and development, including preclinical, clinical and discovery efforts for any future product candidates
- seek regulatory approvals for ETX-810 and ETX-155, or any other product candidates that successfully complete clinical development;
- add operational, financial and management information systems and personnel, including personnel to support our product candidate development and help us comply with our obligations as a public company;
- hire and retain additional personnel, such as clinical, manufacturing, quality control, scientific, commercial and administrative personnel; maintain, expand and protect our intellectual property portfolio;
- establish sales, marketing, distribution, manufacturing, supply chain and other commercial infrastructure in the future to commercialize various products for which we may obtain regulatory approval;
- add equipment and physical infrastructure to support our research and development and growing staff; acquire or in-license other product candidates and technologies; and incur increased costs as a result of operating as a public company.

We expect to rely on capital markets, and to a lesser extent, U.K. research and development tax credits and incentives, for additional funding to conduct our future clinical trials and to complete development and commercialization of our product candidates. If we are unable to access capital when needed, we would be forced to delay, reduce or eliminate our clinical development programs or commercialization efforts.

We had cash, cash equivalents, and marketable securities of $20.5 million and $161.4 million at December 31, 2020 and December 31, 2021, respectively.

Based upon our current operating plan and assumptions, we believe that our existing cash, cash equivalents and marketable securities will be sufficient to fund our operations through late 2023. However, we will need additional capital to complete the clinical development of our product candidates and to commercialize any approved products. Our estimates of the sufficiency of our cash, cash equivalents and marketable securities are based on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we expect. 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.

Conducting clinical trials, pursuing regulatory approvals, establishing outsourced manufacturing relationships and successfully manufacturing and commercializing our product candidates is, and will be, very time-consuming, expensive and an uncertain process that takes years to complete. Our future need for additional funding depends on many factors, including:

- the scope, progress, results and costs of researching and developing ETX-810 and ETX-155 for our initial and potential additional indications, as well as our preclinical product candidates and other future product candidates we may develop;
- the timing and uncertainty of, and the costs involved in, obtaining marketing approvals for ETX-810 and ETX-155 for our initial and potential additional indications and our preclinical product candidates and other future product candidates we may develop and pursue;
- the number of future product candidates that we may pursue and their development requirements; the number of jurisdictions in which we plan to seek regulatory approvals;
- if approved, the costs of commercialization activities for ETX-810 and ETX-155 for any approved indications or any other product candidate that receives regulatory approval to the extent such costs are not the responsibility of any future collaborators, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities;
- subject to receipt of regulatory approval, revenue, if any, received from commercial sales of ETX-810 and ETX-155 for any approved indications or any other product candidates;
- the extent to which we in-license or acquire rights to other products, product candidates or technologies;
- our headcount growth and associated costs as we expand our research and development, establish or increase our office space and establish a commercial infrastructure;
- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights, including enforcing and defending intellectual property related claims;
- any product liability lawsuits related to our products;
- the ongoing costs of operating as a public company; and
- the impact of the COVID-19 pandemic, which may exacerbate the magnitude of the factors discussed above.

We cannot be certain that additional funding will be available on acceptable terms, or at all. Our ability to raise additional capital may be adversely impacted by any disruptions to, or volatility in, the credit and financial markets in the United States and worldwide, including increased volatility in the trading prices for shares of public companies in the biopharmaceutical sector, the ongoing COVID-19 pandemic, or otherwise. We also rely on U.K. research and development tax credits and incentives for funding, and our ability to continue to benefit from such credits and incentives will depend on our ability to continue meet the applicable requirements for them. We have no committed source of additional capital and if we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of our product candidates or other research and development initiatives.

We are in the early stages of clinical drug development and have a very limited operating history and no products approved for commercial sale, which may make it difficult to evaluate our current business and predict our future success and viability.

Drug development is a highly uncertain undertaking and involves a substantial degree of risk. We are conducting multiple Phase 2a clinical trials for our ETX-810 clinical program and plan to initiate Phase 2a and other clinical trials for our ETX-155 clinical program, and have not initiated clinical trials for any of our other current research programs. To date, we have not initiated or completed a pivotal clinical trial, obtained marketing approval for any product candidates, manufactured a commercial scale product or arranged for a third party to do so on our behalf, or conducted sales and marketing activities necessary for successful product commercialization. Our short operating history as a company makes any assessment of our future success and viability subject to significant uncertainty. We will encounter risks and difficulties frequently experienced by early-stage biotechnology companies in rapidly evolving fields, and we have not yet demonstrated an ability to successfully overcome such risks and difficulties. If we do not address these risks and difficulties successfully, our business may be harmed.

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

We have no products approved for commercial sale. To obtain revenues from the sales of our product candidates that are significant or large enough to achieve profitability, we must succeed, either alone or with third parties, in developing, obtaining regulatory approval for, manufacturing and marketing therapies with significant commercial success. Our ability to generate revenue and achieve profitability depends on many factors, including:

- successfully completing preclinical and clinical development of our product candidates; identifying, assessing and/or developing new product candidates;
- developing a sustainable and scalable manufacturing process for our product candidates, as well as establishing and maintaining commercially viable supply relationships with third parties that can provide adequate products and services to support clinical activities and commercial demand for our product candidates;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter;
- obtaining regulatory approvals and marketing authorizations for product candidates for which we successfully complete clinical development;
- launching and successfully commercializing product candidates for which we obtain regulatory and marketing approval, either by establishing a sales, marketing and distribution infrastructure or collaborating with a partner;
- negotiating and maintaining an adequate price for our product candidates, both in the United States and in foreign countries where our products are commercialized;
- satisfying any post-marketing requirements and obtaining reimbursement for its products from private insurance or government payors;
- obtaining market acceptance of our product candidates as viable treatment options;
- building out new facilities or expanding existing facilities to support our ongoing development activity;
- addressing any competing technological and market developments;
- maintaining, protecting, expanding and enforcing our portfolio of intellectual property rights, including patents, trade secrets and know-how; and
- attracting, hiring and retaining qualified personnel.

Because of the numerous risks and uncertainties associated with drug development, we are unable to predict the timing or amount of our expenses, or when we will be able to generate any meaningful revenue or achieve or maintain profitability, if ever. In addition, our expenses could increase beyond our current expectations if we are required by the FDA, or foreign regulatory agencies, to perform studies or clinical trials in addition to those that we currently anticipate, or if there are any delays in any of our or our future collaborators' clinical trials or the development of any of our product candidates. Even if one or more of our product candidates is approved for commercial sale, absent our entering into a collaboration or partnership agreement, we anticipate incurring significant costs associated with commercializing any approved product candidate and ongoing compliance efforts.

Risks Related to our Business and the Development of our Product Candidates

Our business substantially depends upon the successful development of ETX-810 and ETX-155. If we are unable to obtain regulatory approval for, and successfully commercialize, ETX-810 or ETX-155, our business will be harmed.

We currently have no products approved for sale and are investing the majority of our efforts and financial resources in the development of our lead product candidates, ETX-810 for the treatment of diabetic peripheral neuropathic pain and pain associated with lumbosacral radiculopathy, and ETX-155 for the treatment of major depressive disorder, perimenopausal depression and epilepsy. Successful continued development and potential regulatory approval of ETX-810 or ETX-155 for our initial and potential additional indications is critical to the future success of our business. We will need to raise sufficient funds for, and successfully enroll and complete, our clinical development programs of ETX-810 and ETX-155.

Before we can generate any revenue from sales of ETX-810, ETX-155 or any of our other programs, we must undergo additional preclinical and clinical development, regulatory review and approval in one or more jurisdictions. In addition, if one or more of our product candidates are approved, we must ensure access to sufficient commercial manufacturing capacity and conduct significant marketing efforts in connection with any commercial launch. These efforts will require substantial investment, and we may not have the financial resources to continue development of our product candidates or commercialization of any products.

We may experience setbacks that could delay or prevent regulatory approval of our product candidates or our ability to commercialize any products, including:

- negative or inconclusive results from our preclinical studies or clinical trials or the clinical trials of others for product candidates similar to ours, leading to a decision or requirement to conduct additional preclinical testing or clinical trials or abandon a program;
- product-related side effects experienced by subjects in our clinical trials or by individuals using drugs or therapeutics similar to our product candidates;
- delays in submitting investigational new drug applications (INDs) in the United States or comparable foreign applications or delays or failure in obtaining the necessary approvals from regulators or institutional review boards to commence a clinical trial, or a suspension or termination of a clinical trial once commenced;
- if the FDA or comparable foreign authorities do not accept the earlier preclinical and clinical trial work, then we may need to conduct additional preclinical studies or clinical trials beyond that which we currently have planned and significant preclinical study or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our drug candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our drug candidates and may harm our business;
- conditions imposed by the FDA or comparable foreign authorities regarding the scope or design of our clinical trials; delays in contracting with clinical sites or enrolling subjects in clinical trials, including due to the COVID-19 pandemic; delays or interruptions in the supply of materials necessary for the conduct of our clinical trials;
- regulators or institutional review boards (IRBs) or ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- the FDA or other comparable regulatory authorities may disagree with our clinical trial design, including with respect to dosing levels administered in our planned clinical trials, which may delay or prevent us from initiating our clinical trials with our originally intended trial design;
- delays in reaching, or failure to reach, agreement on acceptable terms with prospective trial sites and prospective contract research organizations (CROs) which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- the number of subjects required for clinical trials of any product candidates may be larger than we anticipate or subjects may drop out of these clinical trials or fail to return for post-treatment follow-up at a higher rate than we anticipate;
- our third-party contractors for preclinical studies or clinical trials may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all, or may deviate from the clinical trial protocol or take actions that could cause clinical sites or clinical investigators to drop out of the trial, which may require that we add new clinical trial sites or investigators;

- due to the impact of the COVID-19 pandemic or other events beyond our control, we may experience some delays and interruptions to our preclinical studies and clinical trials, we may experience delays or interruptions to our manufacturing supply chain, or we could suffer delays in reaching, or we may fail to reach, agreement on acceptable terms with third-party service providers on whom we rely;
- greater than anticipated clinical trial costs, including as a result of delays or interruptions that could increase the overall costs to finish our clinical trials as our fixed costs are not substantially reduced during delays;
- we may elect to, or regulators, IRBs, Data Safety Monitoring Boards (DSMBs), or ethics committees may require that we or our investigators, suspend or terminate clinical research or trials for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;
- we may not have the financial resources available to begin and complete the planned trials, or the cost of clinical trials of any product candidates may be greater than we anticipate;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate to initiate or complete a given clinical trial;
- the FDA or other comparable foreign regulatory authorities may require us to submit additional data such as long-term toxicology studies, or impose other requirements before permitting us to initiate a clinical trial, including because the FDA has not reviewed our preclinical or clinical data, to date, having been developed outside the United States;
- inability to compete with other therapies;
- poor efficacy of our product candidates during clinical trials;
- unfavorable FDA or other regulatory agency inspection and review of clinical trial sites or manufacturing facilities;
- unfavorable product labeling associated with any product approvals and any requirements for a Risk Evaluation and Mitigation Strategy (REMS) that may be required by the FDA or comparable requirements in other jurisdictions to ensure the benefits of an individual product outweigh its risks;
- unfavorable acceptance of our clinical trial data by the patient or medical communities or third-party payors;
- failure of our third-party contractors or investigators to comply with regulatory requirements or otherwise meet their contractual obligations in a timely manner, or at all;
- delays related to the impact or the spread of COVID-19 or other pandemics, including the impact of COVID-19 on the FDA's, or similar foreign regulatory agency's, ability to continue its normal operations;
- delays and changes in regulatory requirements, policy and guidelines, including the imposition of additional regulatory oversight around clinical testing generally or with respect to our technology in particular; or
- varying interpretations of data by the FDA and similar foreign regulatory agencies.

We do not have complete control over many of these factors, including certain aspects of clinical development and the regulatory submission process.

For example, in December 2021, we identified metabolites during our analysis of data from our 14-day repeat dose trial of ETX-155. Additional metabolite characterization and qualification work is ongoing. Prior to this unexpected clinical result, we planned to submit an IND application with the FDA in the fourth quarter of 2021 for planned Phase 2a clinical trials of ETX-155 in MDD and PMD. As a result of the identifications of the metabolites, we delayed that submission, including plans to characterize and qualify the metabolites, to the first quarter of 2022.

Furthermore, even if we do receive regulatory approval for ETX-810, ETX-155 or any other potential product candidate we may develop for any indication, any such approval may be subject to limitations on the indications or uses or patient populations for which we may market the product. Accordingly, even if we are able to obtain the requisite financing to continue to fund our development programs, we cannot assure that we will successfully develop or commercialize ETX-810, ETX-155 or any other potential product candidate we may develop for any indication. If we or any of our future collaborators are unable to develop, or obtain regulatory approval for, or, if approved, successfully commercialize ETX-810 or ETX-155 for our initial or potential additional indications, or any other potential product candidate we may develop, we may not be able to generate sufficient revenue to continue our business. In addition, our failure to demonstrate positive results in our clinical trials in any indication for which we are developing ETX-810 and ETX-155 could adversely affect our development efforts for ETX-810 and ETX-155 in other indications.

Preclinical and clinical development involves a lengthy, complex and expensive process with an uncertain outcome. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and the results of our clinical trials may not satisfy the requirements of the FDA or comparable foreign regulatory authorities.

To obtain the requisite regulatory approvals to commercialize any product candidates, we must demonstrate through extensive preclinical studies and clinical trials that our product candidates are safe and effective in humans to the satisfaction of FDA. Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. In particular, in the United States, the general approach for FDA approval of a new drug is dispositive data from two well-controlled, Phase 3 clinical trials of the relevant drug in the relevant patient population. Phase 3 clinical trials typically involve hundreds to thousands of patients, have significant costs and take years to complete. A product candidate can fail at any stage of testing, even after observing promising signs of activity in earlier preclinical studies or clinical trials. The results of preclinical studies and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials. For example, preclinical models evaluating product candidates for pain are notoriously unreliable and, as such, the therapies face substantial translational risk. In addition, initial success in clinical trials may not be indicative of results obtained when such trials are completed. There is typically an extremely high rate of attrition from the failure of product candidates proceeding through clinical trials. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy profile despite having progressed through preclinical studies and initial clinical trials. A number of companies in the biotechnology industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or emergence of unacceptable safety issues, notwithstanding promising results in earlier trials. Most product candidates that commence clinical trials are never approved and there can be no assurance that any of our future clinical trials will ultimately be successful or support further clinical development of ETX-810, ETX-155 or any of our other product candidates. The commencement and rate of completion of preclinical studies and clinical trials may be delayed by many factors, including:

- inability to generate sufficient preclinical or other in vivo or in vitro data to support the initiation of clinical studies;
- preclinical studies or clinical trials may show the product candidates to be less effective than expected (e.g., a clinical trial could fail to meet its primary endpoint(s)) or to have unacceptable side effects or toxicities;
- failure to establish clinical endpoints that applicable regulatory authorities would consider clinically meaningful;
- delays in reaching agreement on acceptable terms with prospective CROs, and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and clinical trial sites;
- delays in identifying, recruiting and training suitable clinical investigators;
- differences in trial design between early-stage clinical trials and later-stage clinical trials make it difficult to extrapolate the results of earlier clinical trials to later clinical trials (e.g., we are basing our therapeutic hypothesis for ETX-810 on studies conducted in the academic setting and the results from the academic studies may not be replicated in a clinical setting);
- delays in recruiting suitable patients to participate in our clinical trials;
- delays in manufacturing, testing, releasing, validating or importing/exporting sufficient stable quantities of our product candidates for use in clinical trials or the inability to do any of the foregoing;
- insufficient or inadequate supply or quality of product candidates or other materials necessary for use in clinical trials, or delays in sufficiently developing, characterizing or controlling a manufacturing process suitable for clinical trials;
- imposition of a temporary or permanent clinical hold by regulatory authorities;
- developments on trials conducted by competitors for related technology that raises FDA or foreign regulatory authority concerns about risk to patients of the technology broadly, or if the FDA or a foreign regulatory authority finds that the investigational protocol or plan is clearly deficient to meet its stated objectives;
- delays in recruiting, screening and enrolling patients and delays caused by patients withdrawing from clinical trials or failing to return for post-treatment follow-up;
- difficulty collaborating with patient groups and investigators;
- failure by our CROs, other third parties or us to adhere to clinical trial protocols;
- failure to perform in accordance with the FDA's or any other regulatory authority's good clinical practice requirements (GCPs) or applicable regulatory guidelines in other countries;
- occurrence of adverse events associated with the product candidate that are viewed to outweigh its potential benefits, or occurrence of adverse events in trial of the same class of agents conducted by other companies;

- the cost of clinical trials of our product candidates being greater than we anticipate;
- clinical trials of our product candidates producing negative or inconclusive results, which may result in our deciding, or regulators requiring us, to conduct additional clinical trials or abandon development of such product candidates;
- transfer of manufacturing processes to larger-scale facilities operated by a third-party contract development and manufacturing organization (CDMO) and delays or failure by our CDMOs or us to make any necessary changes to such manufacturing process; and
- third parties being unwilling or unable to satisfy their contractual obligations to us.

In addition, disruptions caused by the COVID-19 pandemic may increase the likelihood that we encounter such difficulties or delays in initiating, enrolling, conducting or completing our planned and ongoing preclinical studies and clinical trials. Any inability to successfully initiate or complete preclinical studies or clinical trials could result in additional costs to us or impair our ability to generate revenue from product sales. In addition, if we make manufacturing or formulation changes to our product candidates, we may be required to or we may elect to conduct additional studies to bridge our modified product candidates to earlier versions. Clinical trial delays could also shorten any periods during which our products have patent protection and may allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may seriously harm our business.

Further, our current and planned clinical trials do or will contain endpoints that require subjective assessments and subject us to a substantial risk of "placebo effect" which is a well-known risk in clinical trials evaluating therapeutics for pain as well as depression. While a product candidate may show clinical activity or therapeutic benefit, a high placebo effect in a clinical trial will make it difficult to ascertain that benefit or to show statistically significant effect of the product candidate as compared to the control arm and may ultimately cause a clinical trial to fail.

Moreover, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and receive compensation in connection with such services. Under certain circumstances, we may be required to report some of these relationships to the FDA or comparable foreign regulatory authorities. The FDA or comparable foreign regulatory authority may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the study. The FDA or comparable foreign regulatory authority may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA or comparable foreign regulatory authority, as the case may be, and may ultimately lead to the denial of marketing approval of one or more of our product candidates.

Delays in the completion of any preclinical studies or clinical trials of our product candidates will increase our costs, slow down our product candidate development and approval process and delay or potentially jeopardize our ability to commence product sales and generate product revenue. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates. Any delays to our preclinical studies or clinical trials that occur as a result could shorten any period during which we may have the exclusive right to commercialize our product candidates and our competitors may be able to bring products to market before we do, and the commercial viability of our product candidates could be significantly reduced. Any of these occurrences may harm our business, financial condition and prospects significantly.

If we seek to conduct clinical trials in foreign countries or pursue marketing approvals in foreign jurisdictions, we must comply with numerous foreign regulatory requirements governing, among other things, the conduct of clinical trials, manufacturing and marketing authorization, pricing and third-party reimbursement. The foreign regulatory approval process varies among countries and jurisdictions and may include all of the risks associated with FDA approval described above as well as risks attributable to the satisfaction of local regulations in foreign jurisdictions. Moreover, the time required to obtain approval may differ jurisdiction-to-jurisdiction from that required to obtain FDA approval. Approval by foreign regulatory authorities does not ensure approval by the FDA and, similarly, approval by the FDA does not ensure approval by regulatory authorities outside the United States.

Successful completion of clinical trials is a prerequisite to submitting a marketing application to foreign regulatory authorities or the FDA, for each product candidate and, consequently, the ultimate approval and commercial marketing of any product candidates. We may experience negative or inconclusive results, or regulators may be unwilling to accept preclinical or clinical data obtained in foreign jurisdictions, which may result in our deciding, or our being required by regulators, to conduct additional clinical studies or trials or abandon some or all of our product development programs, which could harm our business.

Cross-trial comparisons are not reliable predictors of the relative efficacy of our product candidates against comparators.

We have not conducted head-to-head clinical trials to compare our product candidates with competing products. There are risks associated with comparing the results of our clinical trials with results from other independent studies and trials, as cross-trial comparisons may not be reliable predictors of the relative efficacy or other benefits of our product candidates compared to other product candidates that may be approved or that are in development. Moreover, unless we conduct head-to-head comparative studies, we will not be able to make any claims of superiority even if our products are approved.

Additionally, even though our product candidates are designed to address the same indications as existing therapies, we have not conducted head-to-head clinical trials comparing our product candidates with such existing drugs and therapies. Accordingly, you should consider our prospects in light of the costs, uncertainties, delays and difficulties frequently encountered by clinical and preclinical stage biotechnology companies such as ours.

Public health crises such as pandemics or similar outbreaks could materially and adversely affect our preclinical and clinical trials, business, financial condition and results of operations.

In March 2020, the World Health Organization declared COVID-19 a global pandemic and the United States declared a national emergency with respect to COVID-19. In response to the COVID-19 pandemic, "shelter in place" orders and other public health guidance measures have been implemented across much of the United States and Europe, including in the locations of our offices, clinical trial sites, key vendors and partners. We expect that our clinical development program timelines will be negatively affected by COVID-19, which could materially and adversely affect our business, financial condition and results of operations. Further, due to "shelter in place" orders and other public health guidance measures, we have implemented a work-from-home policy for all staff members excluding those necessary to maintain minimum basic operations. Our increased reliance on personnel working from home may negatively impact productivity, or disrupt, delay or otherwise adversely impact our business. For example, with our personnel working from home, some of our research activities that require our personnel to be in our laboratories will be delayed. We have also experienced delays in availability and shipping of preclinical and clinical supplies and delays in vendor services caused by understaffing or illness. However, to date, these delays have not materially impacted our business.

As a result of the COVID-19 pandemic, or similar pandemics, and related "shelter in place" orders and other public health guidance measures, we have and may in the future experience disruptions that could materially and adversely impact our clinical trials, business, financial condition and results of operations. Potential disruptions include but are not limited to:

- delays or difficulties in enrolling patients in our clinical trials;
- delays or difficulties in initiating or expanding clinical trials, including delays or difficulties with clinical site initiation and recruiting clinical site investigators and clinical site staff;
- increased rates of patients withdrawing from our clinical trials following enrollment as a result of contracting COVID-19or other health conditions or being forced to quarantine;
- interruption of key clinical trial activities, such as clinical trial site data monitoring and efficacy, safety and translational data collection, processing and analyses, due to limitations on travel imposed or recommended by federal, state or local governments, employers and others or interruption of clinical trial subject visits, which may impact the collection and integrity of subject data and clinical study endpoints;
- diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials;
- delays or disruptions in preclinical experiments and IND-enabling studies due to restrictions of on-site staff and unforeseen circumstances at CROs and vendors;
- interruption or delays in the operations of the FDA and comparable foreign regulatory agencies;
- interruption of, or delays in receiving, supplies of our product candidates from our contract manufacturing organizations due to staffing shortages, production slowdowns or stoppages and disruptions in delivery systems;
- delays in receiving approval from local regulatory authorities to initiate our planned clinical trials;
- limitations on employee or other resources that would otherwise be focused on the conduct of our clinical trials and pre-clinical work, including because of sickness of employees or their families, the desire of employees to avoid travel or contact with large groups of people, an increased reliance on working from home, school closures or mass transit disruptions;

- changes in regulations as part of a response to the COVID-19 pandemic which may require us to change the ways in which our clinical trials are conducted, which may result in unexpected costs, or to discontinue the clinical trials altogether;
- delays in necessary interactions with regulators, ethics committees and other important agencies and contractors due to limitations in employee resources or forced furlough of government or contractor personnel; and
- refusal of the FDA to accept data from clinical trials in affected geographies outside the United States.

These and other factors arising from the COVID-19 global pandemic could worsen in countries that are already afflicted with COVID-19, could continue to spread to additional countries or could return to countries where the pandemic has been partially contained, each of which could further adversely impact our ability to conduct clinical trials and our business generally, and could materially and adversely affect our business, financial condition and results of operations.

We may be required to develop and implement additional clinical trial policies and procedures designed to help protect subjects from the COVID-19 virus. For example, in March 2020, the FDA issued a guidance, which FDA subsequently revised, on conducting clinical trials during the pandemic, which describes a number of considerations for sponsors of clinical trials impacted by the pandemic.

The COVID-19 global pandemic continues to rapidly evolve. The extent to which the outbreak may affect our clinical trials, business, financial condition and results of operations will depend on future developments, which are highly uncertain and cannot be predicted at this time, such as the ultimate geographic spread of the disease, the duration of the outbreak, travel restrictions and actions to contain the outbreak or treat its impact, such as social distancing and quarantines or lock-downs in the United States and other countries, business closures or business disruptions and the effectiveness of actions taken in the United States and other countries to contain and treat the disease. Future developments in these and other areas present material uncertainty and risk with respect to our clinical trials, business, financial condition and results of operations.

The trading prices for shares of other biopharmaceutical companies have been highly volatile as a result of the COVID-19 pandemic and, going forward, the trading prices for shares of our common stock could also experience high volatility. As a result, we may face difficulties raising capital through sales of our common stock or such sales may be on unfavorable terms. In addition, a recession, depression or other sustained adverse market event resulting from the spread of the COVID-19 could materially and adversely affect our business and the value of our common stock.

The ultimate impact of the COVID-19 pandemic on our business operations is highly uncertain and subject to change and will depend on future developments, which cannot be accurately predicted, including the duration of the pandemic, the ultimate geographic spread of the disease, additional or modified government actions, new information that will emerge concerning the severity and impact of COVID-19 and the actions taken to contain COVID-19 or address its impact in the short and long term, among others. We do not yet know the full extent of potential delays or impacts on our business, our clinical trials, our research programs, healthcare systems or the global economy. We will continue to monitor the situation closely.

In addition, our business could be materially adversely affected by other business disruptions to us or our third-party providers that could materially adversely affect our potential future revenue and financial condition and increase our costs and expenses. Our operations, and those of our CROs, CDMOs and other contractors, consultants and third parties could be subject to other global pandemics, earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics, geopolitical developments, and other natural or man-made disasters or business interruptions, for which we are predominantly self-insured. For example, the outbreak of war between Russia and Ukraine and the resulting sanctions by U.S. and European governments, together with any additional future sanctions or other actions by them, could have a larger impact that expands into other markets where we do business. Further, the conflict and resulting sanctions or other actions may adversely impact macroeconomic conditions and increase volatility in and affect our ability to access capital markets and external financing sources, as well as have other unforeseen adverse impacts on our business. The occurrence of any of these business disruptions could materially adversely affect our operations and financial condition and increase our costs and expenses. We rely on third-party manufacturers to produce and process our product candidates. Our ability to obtain clinical supplies of our product candidates could be disrupted if the operations of these suppliers are affected by a man-made or natural disaster or other business interruption.

Disruptions at the FDA, the U.S. Securities and Exchange Commission (SEC) and other government agencies caused by funding shortages or global health concerns could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of the SEC and other government agencies on which our operations may rely, including those that fund research and development activities, is subject to the political process, which is inherently fluid and unpredictable.

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

Separately, in response to the COVID-19 pandemic, in March 2020 the FDA announced its intention to postpone most inspections of foreign and domestic manufacturing facilities. In July 2020, the FDA resumed certain on-site inspections 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. Additionally, in April 2021, the FDA issued a guidance document describing its plans to conduct voluntary remote interactive evaluations of certain drug manufacturing facilities and clinical research sites. Remote interactive evaluations may be requested in situations where an in-person inspection would not be prioritized, deemed mission-critical, or where direct inspection is otherwise limited by travel restrictions, but where the FDA determines that remote evaluation would still be appropriate. Regulatory authorities outside the United States have adopted 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.

Our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit their commercial potential or result in significant negative consequences following regulatory approval, if obtained.

Undesirable side effects caused by ETX-810, ETX-155 or any other current or future product candidate could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or comparable foreign regulatory authorities. Results of our clinical trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. In addition, many compounds that have initially showed promise in clinical or earlier stage testing are later found to cause undesirable or unexpected side effects that prevented further development of the compound. For example, our lead preclinical program is a Kv7.2/3 potassium channel opener. This mechanism has been validated through regulatory approvals of multiple first generation Kv7.2/3 openers for the treatment of epilepsy and pain. These molecules showed efficacy but subsequently had to be withdrawn from the market due to significant safety issues. There is no assurance that, if we are able to move our preclinical program forward, we will be able to avoid similar safety problems. Additionally, the composition of our product candidates or learnings in preclinical studies or clinical trials may result in contraindications for any product candidates for which we may obtain regulatory approval.

If unacceptable side effects arise in the development of our product candidates, we may have difficulty recruiting patients to the clinical trials, patients may drop out of our trials, or we may be required to abandon the trials or our development efforts of that product candidate altogether. We, the FDA, other comparable regulatory authorities or IRBs, DSMBs or independent ethics committees at the institutions in which our trials are conducted could suspend or terminate our trials for various reasons, including a belief that subjects in such trials are being exposed to unacceptable health risks or adverse side effects. Some potential therapeutics developed in the biotechnology industry that initially showed therapeutic promise in early-stage trials have later been found to cause side effects that prevented their further development. Even if the side effects do not preclude the product candidate from obtaining or maintaining marketing approval, undesirable side effects may inhibit market acceptance due to its tolerability versus other therapies. Any of these developments could materially adversely affect our business, financial condition and prospects.

Treatment-emergent side effects that are deemed to be drug-related could also result in potential product liability claims. Undesirable side effects in one of our clinical trials (or in a clinical trial of a competitor with a similar mechanism of action) for our product candidates in one indication could adversely affect enrollment in clinical trials, regulatory approval and commercialization of our product candidates in other indications. In addition, these side effects may not be appropriately recognized or managed by the treating medical staff. Any of these occurrences may harm our business.

Moreover, clinical trials of our product candidates are conducted in carefully defined sets of patients who have agreed to enter into clinical trials. Consequently, it is possible that our clinical trials, or those of any future collaborator, 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. Clinical trials by their nature utilize a sample of the potential patient population. With a limited number of patients, rare and severe side effects of our product candidates may only be uncovered with a significantly larger number of patients exposed to the product candidate. If our product candidates receive marketing approval and we or others identify undesirable side effects caused by such product candidates (or any other similar products) after such approval, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw or limit their approval of such product candidates, or seek an injunction against its manufacture or distribution;
- regulatory authorities may require the addition of labeling statements, “boxed” warnings, or issue safety alerts, Dear Healthcare Provider letters, press releases or other communications containing warnings or other safety information about the product;
- we may be required to change the way such product candidates are distributed or administered, or change the labeling of the product candidates;
- the FDA may require a REMS plan to mitigate risks, which could include medication guides, physician communication plans or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools, and regulatory authorities in other jurisdictions may require comparable risk mitigation plans;
- we may be subject to regulatory investigations and government enforcement actions;
- the FDA or a comparable foreign regulatory authority may require us to conduct additional clinical trials or costly post-marketing testing and surveillance to monitor the safety and efficacy of the product;
- we could be sued and held liable for injury caused to individuals exposed to or taking our product candidates; and our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the affected product candidates and could substantially increase the costs of commercializing our product candidates, if approved, and significantly impact our ability to successfully commercialize our product candidates and generate revenues.

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

We may not be able to initiate or continue our planned clinical trials on a timely basis or at all for our product candidates if we are unable to recruit and enroll a sufficient number of eligible patients to participate in these trials through completion of such trials as required by the FDA or other comparable foreign regulatory authorities. Patient enrollment is a significant factor in the timing of clinical trials. Our ability to enroll eligible patients may be limited or may result in slower enrollment than we anticipate. There may be limited patient pools from which to draw for clinical studies. The eligibility criteria of our clinical studies will further limit the pool of available study participants as we will require that patients have specific characteristics that we can measure or to assure their disease is either severe enough or not too advanced to include them in a study. Patient enrollment for our current or any future clinical trials may be affected by other factors, including:

- the patient eligibility criteria defined in the protocol;
- the size of the patient population required for analysis of the trial's primary endpoints;
- the proximity of patients to trial sites;
- the design of the trial;
- the availability and efficacy of approved drugs for the disease under investigation;
- perceived risks and benefits of the product candidate under study;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience;
- competing clinical trials and clinicians' and patients' perceptions as to the potential advantages and risks of the product candidate being studied in relation to other available therapies, including any new drugs that may be approved for the indications that we are investigating;
- clinicians' willingness to screen their patients for biomarkers to indicate which patients may be eligible for enrollment in our clinical trials;
- delays in or temporary suspension of the enrollment of patients in our planned clinical trials due to the COVID-19 pandemic;
- the impacts of the COVID-19 pandemic on clinical trial sites, personnel and patient travel;
- our ability to obtain and maintain patient consents;
- patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment;
- proximity and availability of clinical trial sites for prospective patients; and
- the risk that patients enrolled in clinical trials will drop out of the trials before completion, including as a result of contracting COVID-19 or other health conditions or being forced to quarantine.

In addition, our clinical trials may compete with other clinical trials for product candidates that are in the same therapeutic areas as our product candidates, and this competition would reduce the number and types of patients available to us, because some patients who might have opted to enroll in our trials may instead opt to enroll in a trial being conducted by one of our competitors. Since the number of qualified clinical investigators is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our clinical trials in such clinical trial site.

Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays or might require us to abandon one or more clinical trials altogether. Delays in patient enrollment may result in increased costs, affect the timing or outcome of the planned clinical trials, product candidate development and approval process and jeopardize our ability to seek and obtain the regulatory approval required to commence product sales and generate revenue, which could prevent completion of these trials, adversely affect our ability to advance the development of our product candidates, cause the value of our company to decline and limit our ability to obtain additional financing if needed. Furthermore, even if we are able to enroll a sufficient number of patients for our clinical trials, we may have difficulty maintaining participation in our clinical trials through the treatment and any follow-up periods.

We are also required to register certain clinical trials and post the results of completed clinical trials on a government-sponsored database, such as www.ClinicalTrials.gov in the United States, within certain time frames. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Interim, topline and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available, and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we may publicly disclose preliminary or topline data from our preclinical studies and clinical trials, which is based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the topline or preliminary results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Topline and preliminary data also remain subject to audit and verification procedures that may result in the final data being materially different from the topline or preliminary data we previously published. As a result, topline and preliminary data should be viewed with caution until the final data are available.

From time to time, we may also disclose interim data from our preclinical studies and clinical trials. Interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available or as patients from our clinical trials continue other treatments for their disease. Adverse differences between preliminary or interim data and final data could significantly harm our business prospects. Further, disclosure of interim data by us or by our competitors could result in volatility in the price of our common stock.

Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and our company in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is based on what is typically extensive information, and you or others may not agree with what we determine is material or otherwise appropriate information to include in our disclosure. If the interim, topline or preliminary data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, our product candidates may be harmed, which could harm our business, operating results, prospects or financial condition.

Due to the significant resources required for the development of our pipeline, and depending on our ability to access capital, we must prioritize development of certain product candidates. Moreover, we may fail to expend our limited resources on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

We currently have two lead clinical-stage candidates, ETX-810 and ETX-155. We seek to maintain a process of prioritization and resource allocation to maintain an optimal balance between aggressively advancing product candidates and ensuring replenishment of our portfolio.

Due to the significant resources required for the development of our product candidates, we must focus on specific diseases and disease pathways and decide which product candidates to pursue and advance and the amount of resources to allocate to each. Our decisions concerning the allocation of research, development, collaboration, management, and financial resources toward particular product candidates or therapeutic areas may not lead to the development of any viable commercial product and may divert resources away from better opportunities. If we make incorrect determinations regarding the viability or market potential of any of our product candidates or misread trends in the biotechnology industry, in particular for disorders of the peripheral and central nervous systems, our business may be harmed. As a result, we may fail to capitalize on viable commercial products or profitable market opportunities, be required to forego or delay pursuit of opportunities with other product candidates or other diseases and disease pathways that may later prove to have greater commercial potential than those we choose to pursue, or relinquish valuable rights to such product candidates through collaboration, licensing, or other royalty arrangements in cases in which it would have been advantageous for us to invest additional resources to retain sole development and commercialization rights.

We may not be successful in our efforts to continue to create a pipeline of product candidates or to develop commercially successful products. If we fail to successfully identify and develop additional product candidates, our commercial opportunity may be limited.

One of our strategies is to identify and pursue clinical development of additional product candidates. We currently have novel preclinical candidates in the research, discovery, screening and preclinical stages of development, with two programs currently in advanced discovery stage. Identifying, developing, obtaining regulatory approval and commercializing additional product candidates for the treatment of disorders of the peripheral and central nervous systems will require substantial additional funding and is prone to the risks of failure inherent in drug development. We cannot provide you any assurance that we will be able to successfully identify or acquire additional product candidates, advance any of these additional product candidates through the development process, successfully commercialize any such additional product candidates, if approved, or assemble sufficient resources to identify, acquire, develop or, if approved, commercialize additional product candidates. If we are unable to successfully identify, acquire, develop and commercialize additional product candidates, our commercial opportunity may be limited.

One of the core elements of our strategy is to develop our existing products in multiple indications, also referred to as label expansion. Even if we are successful in developing a product in one indication this does not guarantee that it will be successful in other indications or that we will be able to obtain approval in other patient populations or diseases.

Label expansion is one of the core elements of our strategy. If our current and planned trials are successful, we intend to evaluate additional potential indications for both ETX-810 and ETX-155. For ETX-810, we will explore additional pain indications, which could enable a broad label in peripheral neuropathic pain and chronic pain. For ETX-155, we intend to explore a wide-range of compelling opportunities in both psychiatry and neurology, including potentially generalized anxiety disorder, and bipolar disorder. Even if we are successful in developing a product in one indication does not guarantee that it will be successful in other indications or that we will be able to obtain approval in other patient populations or diseases.

We could be subject to product liability lawsuits based on the use of our product candidates in clinical testing or, if obtained, following our products' marketing approval and commercialization. Product liability lawsuits brought against us or any of our future collaborators could divert our resources and attention, require us to cease clinical testing, cause us to incur substantial liabilities or limit commercialization of our product candidates.

We are exposed to potential product liability and professional indemnity risks that are inherent in the research, development, manufacturing, marketing and use of biotechnology products. Currently, we have no products that have been approved for commercial sale; however, the use of our product candidates by us and any collaborators in clinical trials may expose us to liability claims. We will face an even greater risk if product candidates are approved by regulatory authorities and introduced commercially. Product liability claims may be brought against us or our partners if any product candidate we develop allegedly causes injury or is found to be otherwise unsuitable for human use during product testing, manufacturing, marketing or sale. Any such product liability claim may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability and a breach of warranties. Claims could also be asserted under state consumer protection acts. Such claims could be made by participants enrolled in our clinical trials, patients, health care providers, biotechnology companies, our collaborators or others using, administering or selling any of our future approved products. If we cannot successfully defend ourselves against any such claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense would require significant financial and management resources.

Regardless of the merits or eventual outcome, product liability claims may result in:

- decreased demand for any of our future approved products;
- injury to our reputation;
- withdrawal of clinical trial participants;
- termination of clinical trial sites or entire trial programs;
- significant litigation costs;
- substantial monetary awards to, or costly settlements with, patients or other claimants;
- product recalls or a change in the indications for which any approved drug products may be used;
- loss of revenue;

- diversion of management and scientific resources from our business operations; and
- the inability to commercialize our product candidates.

Although the clinical trial process is designed to identify and assess potential side effects, clinical development does not always fully characterize the safety and efficacy profile of a new medicine, and it is always possible that a drug, even after regulatory approval, may exhibit unforeseen side effects. If our product candidates were to cause adverse side effects during clinical trials or after approval, we may be exposed to substantial liabilities. Physicians and patients may not comply with any warnings that identify known potential adverse effects and patients who should not use our product candidates. If any of our product candidates are approved for commercial sale, we will be highly dependent upon consumer perceptions of us and the safety and quality of our products. We could be adversely affected if we are subject to negative publicity associated with illness or other adverse effects resulting from physicians' or patients' use or misuse of our products or any similar products distributed by other companies.

Although we maintain product liability insurance coverage including clinical trial liability, this insurance may not fully cover potential liabilities that we may incur. The cost of any product 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 regulatory approval. In addition, insurance coverage is becoming increasingly expensive. If we are unable to maintain sufficient insurance coverage at an acceptable cost or to otherwise protect against potential product liability claims, it could prevent or inhibit the development and commercial production and sale of our product candidates, which could harm our business.

Risks Related to Legal and Regulatory Compliance

Enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval and commercialize our product candidates and may affect the prices we may charge for such product candidates.

The United States and many foreign jurisdictions have enacted or proposed legislative and regulatory changes affecting the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product for which we obtain marketing approval.

In March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, the Affordable Care Act (ACA), was enacted, which includes measures that have significantly changed the way health care is financed by both governmental and private insurers. There have been executive, judicial and congressional challenges to certain aspects of the ACA. On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court's decision, President Biden issued an executive order that initiated a special enrollment period for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is unclear how the Supreme Court ruling, other such litigation, and the healthcare reform measures of the Biden administration will impact the ACA. We continue to evaluate the effect that the ACA and its possible repeal and replacement has on our business.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. For example, in August 2011, the Budget Control Act of 2011 was signed into law, which, among other things, included aggregate reductions to Medicare payments to providers of, on average, 2% per fiscal year, effective April 1, 2013, which, due to subsequent legislative amendments including the Infrastructure Investment and Jobs Act, will stay in effect through 2031 with the exception of a temporary suspension from May 1, 2020 through March 31, 2022 due to the COVID-19 pandemic, unless Congress takes additional action. Under current legislation the actual reduction in Medicare payments will vary from 1% in 2022 to up to 3% in the final fiscal year of this sequester. Recently, there has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. presidential executive orders, congressional inquiries and legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs and reform government program reimbursement methodologies for drugs. At the federal level, the Biden administration used several means to propose or implement drug pricing reform, including through executive orders and policy initiatives. For example, in July 2021, the Biden administration released an executive order, "Promoting Competition in the American Economy," with multiple provisions aimed at prescription drugs. In response to Biden's executive order, on September 9, 2021, U.S. Department of Health and Human Services (HHS) released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue to advance these principles. No legislation or administrative actions have been finalized to implement these principles. In addition, Congress is considering drug pricing as part of other reform initiatives. It is unclear whether these or similar policy initiatives will be implemented in the future. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control costs for pharmaceutical and biological products. It is also possible that additional governmental action will be taken in response to the COVID-19 pandemic.

We expect that the healthcare reform measures that have been adopted and may be adopted in the future may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product and could seriously harm our future revenues. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our products.

Our business operations and current and future relationships with investigators, health care professionals, consultants, third-party payors and customers will be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws and other healthcare laws and regulations. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

Healthcare providers and others play a primary role in the recommendation and prescription of any products for which we obtain marketing approval. Although we do not currently have any products on the market, our operations may be, directly or indirectly through our prescribers, customers and third-party payors, subject to various U.S. federal and state healthcare laws and regulations. These laws may impact, among other things, our current business operations, including our clinical research activities and proposed sales, marketing and education programs and constrain the business of financial arrangements and relationships with healthcare providers and other parties through which we may market, sell and distribute our products for which we obtain marketing approval. In addition, we may be subject to additional healthcare, statutory and regulatory requirements and enforcement by foreign regulatory authorities in jurisdictions in which we conduct our business. The laws that may affect our ability to operate include:

- the U.S. federal Anti-Kickback Statute, which makes it illegal for any person or entity, including a prescription drug manufacturer (or a party acting on its behalf), to knowingly and willfully solicit, receive, offer or pay any remuneration (including any kickback, bribe, or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual, or the purchase, lease, order, arrangement, or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

- the U.S. federal civil and criminal false claims laws, including the False Claims Act (FCA), which can be enforced through "qui tam" or "whistleblower" actions, and civil monetary penalty law, which impose criminal and civil penalties against individuals or entities for, among other things, knowingly presenting, or causing to be presented, claims for payment or approval from Medicare, Medicaid, or other federal health care programs that are false, fictitious or fraudulent; knowingly making, using, or causing to be made or used, a false record or statement material to a false, fictitious or fraudulent claim or an obligation to pay or transmit money or property to the federal government; or knowingly concealing or knowingly and improperly avoiding or decreasing or concealing such an obligation to pay money to the federal government. In addition, a claim that includes items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim under the FCA;
- the U.S. federal Health Insurance Portability and Accountability Act of 1996 (HIPAA), which created additional federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payors, or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false, fictitious or fraudulent statement or representation, or making or using any false writing or document knowing the same to contain any materially false fictitious or fraudulent statement or entry in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters. Similar to the federal Anti-Kickback Statute, a person or entity can be found guilty of violating HIPAA fraud provisions without actual knowledge of the statute or specific intent to violate it;
- the U.S. federal Physician Payments Sunshine Act and its implementing regulations, which require certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program to report annually to the Centers for Medicare and Medicaid Services (CMS) an agency within the HHS under the Open Payments Program, information related to direct or indirect payments and other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), other health care professionals (such as physician assistants and nurse practitioners), and teaching hospitals, as well as information regarding ownership and investment interests held by physicians and their immediate family members;
- U.S. federal and state consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers;
- analogous U.S. state laws and regulations, including state anti-kickback and false claims laws that may apply to items or services reimbursed by any third-party payor, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and other relevant compliance guidance promulgated by the federal government that otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to file reports with states regarding pricing and marketing information, such as the tracking and reporting of gifts, compensations and other remuneration and items of value provided to healthcare professionals and entities; and state and local laws requiring the registration of pharmaceutical sales representatives; and
- European and other foreign law equivalents of each of the laws, including reporting requirements detailing interactions with and payments to healthcare providers.

Ensuring that our internal operations and future business arrangements with third parties comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations, agency guidance or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of the laws described above or any other governmental laws and regulations that may apply to us, we may be subject to significant penalties, including civil, criminal and administrative penalties, damages, fines, exclusion from U.S. government funded healthcare programs, such as Medicare and Medicaid, or similar programs in other countries or jurisdictions, disgorgement, imprisonment, contractual damages, reputational harm, diminished profits, 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 and the delay, reduction, termination or restructuring of our operations. Further, defending against any such actions can be costly and 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. If any of the physicians or other providers or entities with whom we expect to do business is found to not be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs and imprisonment. If any of the above occur, it could adversely affect our ability to operate our business and our results of operations.

We are subject to stringent and changing obligations related to data privacy and security. Our actual or perceived failure to comply with such obligations could lead to regulatory investigations or actions; litigation; fines and penalties; disruptions of our business operations; reputational harm; loss of revenue or profits; loss of customers or sales; and other adverse business consequences.

We process personal data and other sensitive data (including health data we collect about trial participants in connection with clinical trials); proprietary and confidential business data; trade secrets; intellectual property; and sensitive third-party data. Our data processing activities subject us to numerous data privacy and security obligations, such as various laws, regulations, guidance, industry standards, external and internal privacy and security policies, contracts, and other obligations that govern the processing of personal data by us and on our behalf.

In the United States, federal, state, and local governments have enacted numerous data privacy and security laws, including data breach notification laws, personal data privacy laws, and consumer protection laws. These privacy laws include, without limitation, the following laws and regulations: Section 5 of the Federal Trade Commission Act, the Health Insurance Portability and Accountability Act of 1996 (HIPAA) as amended by the Health Information Technology for Economic and Clinical Health Act (HITECH) (which imposes specific requirements relating to the privacy, security and transmission of individually identifiable health information) and the California Consumer Privacy Act of 2018 (CCPA) (which imposes specific requirements on covered businesses relating to personal data practices). If we are or were to become subject to these laws and/or new or amended data privacy laws, the risk of enforcement actions against us could increase because we may be subject to obligations under applicable regulatory frameworks and the number of individuals or entities that could initiate actions against us may increase (including individuals via a private right of action), in addition to further complicating our compliance efforts.

Outside the United States, an increasing number of laws, regulations, and industry standards apply to data privacy and security. For example, the European Union's General Data Protection Regulation (EU GDPR) and the equivalent law in the United Kingdom (UK GDPR) impose strict requirements for processing the personal data of individuals, including sensitive data that we may process such as health data. For example, under the EU GDPR, government regulators may impose temporary or definitive bans on data processing, as well as fines of up to 20 million euros or 4% of annual global revenue, whichever is greater. Similar processing penalties and fines exist under the UK GDPR and the uncertainty of data protection laws in the UK following Brexit has increased the complexity of our compliance efforts. Further, individuals may initiate litigation related to our processing of their personal data.

Certain jurisdictions have enacted data localization laws and cross-border personal data transfer laws. For example, absent appropriate safeguards or other circumstances, the EU GDPR, UK GDPR, and laws in Switzerland generally restrict the transfer of personal data to countries such as the United States that do not provide an adequate level of personal data protection. The European Commission released a set of "Standard Contractual Clauses" that are designed to be a valid mechanism by which entities can transfer personal data out of the European Economic Area (EEA) to jurisdictions that the European Commission has not found to provide an adequate level of protection. Currently, these Standard Contractual Clauses are a valid mechanism to transfer personal data outside of the EEA. The Standard Contractual Clauses, however, require parties that rely upon that legal mechanism to comply with additional obligations, such as conducting transfer impact assessments to determine whether additional security measures are necessary to protect the at-issue personal data. Moreover, due to potential legal challenges, there exists some uncertainty regarding whether the Standard Contractual Clauses will remain a valid mechanism for transfers of personal data out of the EEA. Similar restrictions and transfer mechanisms exist under the UK GDPR. Any of these restrictions and obligations could increase the cost and complexity of doing business in foreign jurisdictions. If we cannot implement valid compliance mechanisms for cross-border personal data transfers, we may face increased exposure to regulatory actions, substantial fines, and injunctions against processing or transferring personal data from Europe or elsewhere. The inability to import personal data to the United States could significantly and negatively impact our business operations, including by limiting our ability to conduct clinical trial activities in Europe, the United Kingdom and elsewhere; limiting our ability to collaborate with parties that are subject to European and other data privacy and security laws; or requiring us to increase our personal data processing capabilities and infrastructure in Europe and/or elsewhere at significant expense.

Our obligations related to data privacy and security are quickly changing in an increasingly stringent fashion, creating some uncertainty as to the effective future legal framework. Additionally, these obligations may be subject to differing applications and interpretations, which may be inconsistent or in conflict among jurisdictions. Preparation for and compliance with these obligations requires us to devote significant resources (including, without limitation, financial and time-related resources). These obligations may necessitate changes to our information technologies, systems, and practices and to those of any third parties that process personal data on our behalf. Although we endeavor to comply with all applicable data privacy and security obligations, we may at times fail (or be perceived to have failed) to do so. Despite our efforts, our personnel or third parties upon whom we rely may fail to comply with such obligations, which could negatively impact our business operations and compliance posture. For example, any failure by a third-party processor to comply with applicable law, regulations, or contractual obligations could result in adverse effects, including inability to operate our business and proceedings against us by governmental entities or others. Moreover, clinical trial subjects about whom we or our potential collaborators obtain information, as well as the third-party providers (such as research institutions) who share this information with us, may contractually limit our ability to use and disclose the information.

If we fail, or are perceived to have failed, to address or comply with data privacy and security obligations, we could face significant consequences. These consequences may include, but are not limited to, government enforcement actions (e.g., investigations, fines, penalties, audits, inspections, and similar); litigation (including class-related claims); additional reporting requirements and/or oversight; bans on processing personal data; and orders to destroy or not use personal data. Any of these events could have a material adverse effect on our reputation, business, or financial condition, including but not limited to: loss of customers; interruptions or stoppages in our business operations (including our clinical trials); inability to process personal data or to operate in certain jurisdictions; limited ability to develop or commercialize our product candidates; expenditure of time and resources to defend any claim or inquiry; adverse publicity; or revision or restructuring of our operations.

Further, the vote in the United Kingdom in favor of exiting the EU, referred to as Brexit, has created uncertainty with regard to data protection regulation in the United Kingdom. From January 1, 2021, companies have to comply with the GDPR and also the United Kingdom GDPR (U.K. GDPR), which, together with the amended U.K. Data Protection Act 2018, retains the GDPR in U.K. national law. The U.K. GDPR mirrors the fines under the GDPR, i.e., fines up to the greater of €20 million (£17.5 million) or 4% of global turnover. The relationship between the United Kingdom and the European Union (EU), in relation to certain aspects of data protection law remains unclear, and it is unclear how United Kingdom data protection laws and regulations will develop in the medium to longer term, and how data transfers to and from the United Kingdom will be regulated in the long term. These changes will lead to additional costs and increase our overall risk exposure. Currently there is a four to six-month grace period agreed in the EU and United Kingdom Trade and Cooperation Agreement, ending June 30, 2021 at the latest, whilst the parties discuss an adequacy decision. The European Commission published a draft adequacy decision on February 19, 2021. If adopted, the decision will enable data transfers from EU member states to the United Kingdom for a four-year period, subject to subsequent extensions.

Although we work to comply with applicable laws, regulations and standards, our contractual obligations and other legal obligations, these requirements are evolving and may be modified, interpreted and applied in an inconsistent manner from one jurisdiction to another, and may conflict with one another or other legal obligations with which we must comply. Compliance with U.S. and foreign data protection laws and regulations could require us to take on more onerous obligations in our contracts, restrict our ability to collect, use and disclose data, or in some cases, impact our ability to operate in certain jurisdictions. Failure by us or our collaborators and third-party providers to comply with U.S. and foreign data protection laws and regulations could result in government enforcement actions (which could include civil or criminal penalties), private litigation and/or adverse publicity and could negatively affect our operating results and business. Moreover, clinical trial subjects about whom we or our potential collaborators obtain information, as well as the providers who share this information with us, may contractually limit our ability to use and disclose the information. Claims that we have violated individuals' privacy rights, failed to comply with data protection laws or breached our contractual obligations, even if we are not found liable, could be expensive and time consuming to defend, could result in adverse publicity and could harm our business.

Risks Related to Commercialization of our Product Candidates

We have never commercialized a product candidate and we may lack the necessary expertise, personnel and resources to successfully commercialize any of our products that receive regulatory approval on our own or together with collaborators.

We have never commercialized a product candidate. Our operations to date have been limited to organizing and staffing our company, business planning, raising capital, and undertaking preclinical studies and clinical trials of our product candidates. We currently have no sales force, marketing, manufacturing or distribution capabilities. To achieve commercial success of our product candidates, if any are approved, we will have to develop our own sales, marketing, reimbursement and manufacturing capabilities or outsource these activities to a third party.

Factors that may affect our ability to commercialize our product candidates on our own include recruiting and retaining adequate numbers of effective sales and marketing personnel, persuading adequate numbers of physicians to prescribe our product candidates and other unforeseen costs associated with creating an independent sales and marketing organization. Developing a sales and marketing organization requires significant investment, is time-consuming and could delay the launch of our product candidates. We may not be able to build an effective sales and marketing organization in the United States, the European Union or other key global markets. If we are unable to build our own distribution and marketing capabilities or to find suitable partners for the commercialization of our product candidates, we may have difficulties generating revenue from them.

We face significant competition from other pharmaceutical and biotechnology companies and other research organizations, and our operating results will suffer if we fail to compete effectively.

The biotechnology industry is characterized by rapid technological advancement, significant competition and an emphasis on intellectual property. We face potential competition from many different sources, including major and specialty pharmaceutical, biopharmaceutical, and biotechnology companies, and public and private research institutions. Any product candidates that we successfully develop and commercialize will compete with current therapies and new therapies that may become available in the future. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective or more convenient or have fewer or less severe side effects than any products that we may develop. Our competitors also may obtain FDA, EMA or other regulatory approval for their products more rapidly than we do.

We expect to face competition from existing products and products in development for each of our product candidates. In addition, there may be other earlier stage clinical programs that, if approved, would compete with our product candidates. Many of our competitors have substantially greater financial, technical, manufacturing, marketing, sales and supply resources or experience than we do. Additional mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated in our competitors. Competition may increase further as a result of advances made in the commercial applicability of technologies and greater availability of capital for investment in these fields.

Because ETX-810 is a prodrug of PEA, an endogenous bioactive lipid, which is already marketed by other companies in various formulations as medical foods, nutraceuticals and dietary supplements, we may be exposed to unique risk related to non-prescription competition and consumer substitution.

ETX-810 is a prodrug of PEA, an endogenous bioactive lipid. Various formulations of PEA are currently marketed by others as medical foods, nutraceuticals and dietary supplements. We believe that ETX-810, if approved, will have a superior therapeutic profile to dietary supplement PEA available. However, we cannot be sure physicians and patients will view ETX-810, if approved, as superior. To the extent the price of ETX-810, if approved, is significantly higher than the prices of dietary supplement PEA, physicians may recommend these commercial alternatives instead of writing prescriptions for ETX-810, or patients may elect on their own to take dietary supplement PEA products. Additionally, negative experiences with dietary supplement PEA may have an adverse impact on our ability to obtain regulatory approval, or if we obtain such approval, on demand for our products. Either of these outcomes may adversely impact our results of operations by limiting how we price our product. Additionally, any adverse effects experienced by the users of dietary supplement PEA could adversely impact the regulatory approval process for ETX-810 or physician or patient demand for ETX-810, even if we are successful in obtaining regulatory approval for and commercialization of such product candidate.

In addition, because current formulations of PEA are only available as dietary supplements, the precedent body of data regarding PEA is based exclusively on studies of PEA in its dietary supplement formulations. There can be no assurance that ETX-810 will achieve the same or similar results in clinical testing as observed in these studies of PEA in its dietary supplement formulations.

The successful commercialization of certain of our product candidates will depend in part on the extent to which governmental authorities and health insurers establish adequate coverage, reimbursement levels and pricing policies. Failure to obtain or maintain adequate coverage and reimbursement for our product candidates, if approved, could limit our ability to market those products and decrease our ability to generate revenue.

The availability and adequacy of coverage and reimbursement by governmental healthcare programs such as Medicare and Medicaid, private health insurers and other third-party payors are essential for most patients to be able to afford products such as our product candidates, if approved. Our ability to achieve acceptable levels of coverage and reimbursement for products by governmental authorities, private health insurers and other organizations will have an effect on our ability to successfully commercialize our product candidates and attract additional collaboration partners to invest in the development of our product candidates. Coverage under certain government programs, such as Medicare, Medicaid, the 340B drug pricing program and TRICARE, may not be available for certain of our product candidates. Assuming we obtain coverage for a given product by a third-party payor, the resulting reimbursement payment rates may not be adequate or may require co-payments that patients find unacceptably high. We cannot be sure that coverage and reimbursement in the United States, the European Union or elsewhere will be available for any product that we may develop, and any reimbursement that may become available may be decreased or eliminated in the future.

Third-party payors increasingly are challenging prices charged for pharmaceutical products and services, and many third-party payors may refuse to provide coverage and reimbursement for particular drugs when an equivalent generic drug, biosimilar or a less expensive therapy is available. It is possible that a third-party payor may consider our product candidates and other therapies as substitutable and only offer to reimburse patients for the less expensive product. Even if we show improved efficacy or improved convenience of administration with our product candidates, pricing of existing drugs may limit the amount we will be able to charge for our product candidates. These payors may deny or revoke the reimbursement status of a given product or establish prices for new or existing marketed products at levels that are too low to enable us to realize an appropriate return on our investment in product development. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize our product candidates, and may not be able to obtain a satisfactory financial return on products that we may develop.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, third-party payors, including private and governmental payors, such as the Medicare and Medicaid programs, play an important role in determining the extent to which new drugs and biologics will be covered. The Medicare and Medicaid programs increasingly are used as models for how private payors and other governmental payors develop their coverage and reimbursement policies for drugs and biologics. Some third-party payors may require pre-approval of coverage for new or innovative devices or drug therapies before they will reimburse health care providers who use such therapies. It is difficult to predict at this time what third-party payors will decide with respect to the coverage and reimbursement for our product candidates.

Obtaining and maintaining reimbursement status is time-consuming and costly. No uniform policy for coverage and reimbursement for products exists among third-party payors in the United States. Therefore, 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 our products to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance. Furthermore, rules and regulations regarding reimbursement change frequently, in some cases at short notice, and we believe that changes in these rules and regulations are likely.

Moreover, increasing efforts by governmental and third-party payors in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for newly approved products and, as a result, they may not cover or provide adequate payment for our product candidates. We expect to experience pricing pressures in connection with the sale of any of our product candidates due to the trend toward managed healthcare, the increasing influence of health maintenance organizations, and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. The continuing efforts of the government, insurance companies, managed care organizations and other payors of health care services to contain or reduce costs of health care may adversely affect:

- the demand for any products for which we may obtain regulatory approval;
- our ability to set a price that we believe is fair for our products;
- our ability to obtain coverage and reimbursement approval for a product;
- our ability to generate revenues and achieve or maintain profitability; and
- the level of taxes that we are required to pay.

If we are unable to establish or sustain coverage and adequate reimbursement for any product candidates from third-party payors, the adoption of those products and sales revenue will be adversely affected, which, in turn, could adversely affect the ability to market or sell those product candidates, if approved. Further, coverage policies and third-party payor reimbursement rates may change at any time. Therefore, even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Even if we receive marketing approval for any of our product candidates, we may not achieve market acceptance, which would limit the revenue that we can generate from sales of any of our approved product candidates.

Even if the FDA or any comparable foreign regulatory authority approves the marketing of any product candidates that we develop, physicians, patients, third-party payors or the medical community may not accept or use them. Efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may not be successful. Market acceptance of ETX-810, ETX-155 and our other product candidates, if any are approved, will depend on a number of factors, including, among others:

- the ability of ETX-810, ETX-155 and our other product candidates to treat neuronal excitability disorders, as compared with other available drugs, treatments or therapies;
- the prevalence and severity of any adverse side effects associated with ETX-810, ETX-155 and our other future product candidates;
- limitations or warnings contained in the labeling approved for ETX-810, ETX-155 or our other future product candidates by the FDA or any comparable foreign regulatory authority;
- availability of alternative treatments;
- the size of the target patient population, and the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support and timing of market introduction of competitive products;
- publicity for our product candidates and competing products and treatments;
- pricing and cost effectiveness;
- the effectiveness of our sales and marketing strategies;
- our ability to increase awareness of our product candidates through marketing efforts;
- our ability to obtain sufficient third-party coverage and adequate reimbursement; and
- the likelihood that the FDA or any comparable foreign regulatory authority may impose additional requirements that limit the promotion, advertising, distribution or sales of our product candidates.

If any one of our product candidates is approved but does not achieve an adequate level of acceptance by patients, physicians and third-party payors, we may not generate sufficient revenue to become or remain profitable and our business may be harmed.

If any of our product candidates are approved for marketing and commercialization and we are unable to establish sales, marketing and market access capabilities or enter into agreements with third parties to sell and market our product candidates, we will be unable to successfully commercialize our product candidates if and when they are approved.

We currently have no sales, marketing, reimbursement or distribution capabilities. To achieve commercial success for any approved product for which we retain sales, marketing and market access and reimbursement responsibilities, we must either develop these capabilities, which would be expensive and time consuming, or outsource these functions to other third parties, some or all of which may be occur in advance of any approval of the product candidate. In the future, we may choose to build a focused sales and marketing infrastructure to sell, or participate in sales activities with any future collaborators for, some of our product candidates if and when they are approved.

There are risks involved with both establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force is expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

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

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or educate adequate numbers of physicians on the benefits of prescribing any future product candidates;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we enter into arrangements with third parties to perform sales, marketing and distribution services, our product revenues or the profitability of these product revenues to us are likely to be lower than if we were to market and sell any products that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell and market our product candidates or may be unable to do so on terms that are favorable to us. In entering into third-party marketing or distribution arrangements, any revenue we receive will depend upon the efforts of the third parties and we cannot assure you that such third parties will establish adequate sales and distribution capabilities or devote the necessary resources and attention to sell and market our product candidates effectively. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

Risks Related to our Dependence on Third Parties

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

We rely on third-party CROs to conduct, supervise, and monitor our preclinical studies and certain clinical trials for our product candidates and do not currently plan to independently conduct preclinical studies or clinical trials of any other potential product candidates. We expect to continue to rely on third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators to conduct our preclinical studies and clinical trials. While we have agreements governing their activities, we have limited influence over their actual performance and control only certain aspects of their activities. The failure of these third parties to successfully carry out their contractual duties or meet expected deadlines could substantially harm our business because we may not obtain marketing approval for or commercialize our product candidates in a timely manner or at all. Moreover, these agreements might terminate for a variety of reasons, including a failure to perform by the third parties. If we need to enter into alternative arrangements, that would delay our product development activities and harm our business.

Our reliance on these third parties for development activities will reduce our control over these activities. Nevertheless, we are responsible for ensuring that each of our studies and clinical trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards and our reliance on the CROs does not relieve us of our regulatory responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial and for ensuring that our preclinical trials are conducted in accordance with good laboratory practice, or GLP, as appropriate. Moreover, the FDA and comparable foreign regulatory authorities require us to comply with standards, commonly referred to as good clinical practices, or GCPs, for conducting, monitoring, 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 trial participants are protected. As a clinical trial sponsor, we also have regulatory requirements that directly apply to us. Regulatory authorities enforce these requirements through periodic inspections of trial sponsors, clinical investigators, and trial sites. If we or any of our CROs fail to comply with applicable GCPs, we or our CROs may be subject to enforcement or other legal actions, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials.

In addition, once we have an approved product, we will be required to report certain financial interests of our third-party investigators if these relationships exceed certain financial thresholds or meet other criteria. The FDA and comparable foreign regulatory authorities may question the integrity of the data from those clinical trials conducted by investigators who previously served or currently serve as scientific advisors or consultants to us from time to time and receive cash compensation in connection with such services or otherwise receive compensation from us that could be deemed to impact study outcome, proprietary interests in a product candidate, certain company equity interests or significant payments of other sorts.

We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials complies with GCP regulations. In addition, our clinical trials must be conducted with product candidates that were produced under current Good Manufacturing Process (cGMP) regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. We also are required to register certain clinical trials and post the results of certain completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within specified time frames. Failure to do so can result in enforcement actions and adverse publicity.

Our CROs may also have relationships with other entities, some of which may be our competitors, for whom they may also be conducting clinical trials or other drug development activities that could harm our competitive position. In addition, our CROs are not our employees, and except for remedies available to us under our agreements with such CROs, we cannot control whether or not they devote sufficient time and resources to our ongoing clinical, non-clinical, and preclinical programs. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our preclinical studies or clinical trials in accordance with regulatory requirements or our stated protocols, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates, or we or they may be subject to regulatory enforcement actions. As a result, our results of operations and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed. To the extent we are unable to successfully identify and manage the performance of third-party service providers in the future, our business may be harmed.

If any of our relationships with these third-party CROs terminates, we may not be able to enter into arrangements with alternative CROs or to do so on commercially reasonable terms. Switching or adding additional CROs involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays could occur, which could compromise our ability to meet our desired development timelines. Though we carefully manage our relationships with our CROs, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not harm our business.

If the manufacturers upon whom we rely fail to produce our product candidates in the volumes that we require on a timely basis, or to comply with stringent regulations applicable to pharmaceutical drug manufacturers, we may face delays in the development and commercialization of, or be unable to meet demand for, our products and may lose potential revenues.

We do not manufacture any of our product candidates, and we do not currently plan to develop any capacity to do so. We currently outsource all manufacturing of our product candidates to third-party CDMOs, typically without any guarantee that there will be sufficient supplies to fulfill our requirements or that we may obtain such supplies on acceptable terms. Any delays in obtaining adequate supplies with respect to our product candidates may delay the development or commercialization of our product candidates.

We may not succeed in our efforts to establish manufacturing relationships or other alternative arrangements for any of our existing or future product candidates and programs. Our product candidates may compete with other products and product candidates for access to manufacturing facilities. There are a limited number of CDMOs that operate under cGMP regulations and that are both capable of manufacturing for us and willing to do so. If our existing third-party manufacturers, or the third parties that we engage in the future to manufacture a product for commercial sale or for our clinical trials, should cease to continue to do so for any reason, we likely would experience delays in obtaining sufficient quantities of our product candidates for us to meet commercial demand or to advance our clinical trials while we identify and qualify replacement suppliers. If for any reason we are unable to obtain adequate supplies of our product candidates or the raw materials used to manufacture them, it will be more difficult for us to develop our product candidates and compete effectively. Further, even if we do establish such collaborations or arrangements, our third-party manufacturers may breach, terminate or not renew these agreements.

We have a limited number of contract manufacturers for our product candidates. At times we may have only one manufacturer for a product. In addition, we do not have any long-term commitments from our suppliers of clinical trial material or guaranteed prices for our product candidates. The manufacture of pharmaceutical products requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of pharmaceutical products often encounter difficulties in production, particularly in scaling up initial production. These problems include difficulties with production costs and yields; quality control, including stability of the product candidate and quality assurance testing; shortages of qualified personnel; and compliance with strictly enforced federal, state, and foreign regulations. Our manufacturers may not perform as agreed. If our manufacturers were to encounter any of these difficulties, our ability to provide product candidates to patients in our clinical trials and for commercial use, if approved, would be jeopardized.

In addition, all manufacturers of our product candidates must comply with cGMP requirements enforced by the FDA and comparable foreign regulatory authorities that are applicable to both finished drug products and active pharmaceutical ingredients used both for clinical and commercial supply, through its facilities inspection program. The FDA must verify our contract manufacturers' compliance with cGMP requirements and comparable foreign regulatory authorities will similarly inspect our contract manufacturers' facilities after we submit our marketing applications to the agency and comparable foreign regulatory authorities. The cGMP requirements include quality control, quality assurance, and the maintenance of records and documentation. Manufacturers of our product candidates may be unable to comply with our specifications, these cGMP requirements and with other FDA, state, and foreign regulatory requirements. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or other regulatory authorities, they will not be able to secure or maintain regulatory approval for their manufacturing facilities. While we are ultimately responsible for the manufacture of our product candidates, other than through our contractual arrangements, we have little control over our manufacturers' compliance with these regulations and standards. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for, or market our product candidates, if approved. A failure to comply with these requirements may result in regulatory enforcement actions against our manufacturers or us, including fines and civil and criminal penalties, including imprisonment; suspension or restrictions of production; suspension, delay, or denial of product approval or supplements to approved products; clinical holds or termination of clinical studies; warning or untitled letters; regulatory authority communications warning the public about safety issues with the drug; refusal to permit the import or export of the products; product seizure, detention, or recall; civil suits under the FCA; corporate integrity agreements; consent decrees; or withdrawal of product approval. If the safety of any quantities supplied is compromised due to our manufacturers' failure to adhere to applicable laws or for other reasons, we may not be able to obtain regulatory approval for or successfully commercialize our product candidates.

Any failure or refusal to supply our product candidates or components for our current or future product candidates that we may develop could delay, prevent, or impair our clinical development or commercialization efforts. Any change in our manufacturers could be costly because the commercial terms of any new arrangement could be less favorable and because the expenses relating to the transfer of necessary technology and processes could be significant.

If we are not able to establish future collaborations, we may have to alter some of our future development and commercialization plans.

Our product development programs and the potential commercialization of our product candidates will require substantial additional capital to fund expenses. While currently we have no plans to do so, we may decide to collaborate for the future development and potential commercialization of our product candidates. Furthermore, we may find that our programs require the use of proprietary rights held by third parties, and the growth of our business may depend in part on our ability to acquire, in-license or use these proprietary rights. We will likely have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of any product candidates we may seek to develop with them. We cannot predict the success of any collaboration that we have entered into or will enter into.

We face significant competition in seeking appropriate collaborators, and a number of more established companies may also be pursuing strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, financial resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA, European Medicines Agency (EMA), the U.K. Medicines and Healthcare products Regulatory Agency (MHRA) or similar foreign regulatory authorities, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge, and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for our product candidate. We may also be restricted under future license agreements from entering into agreements on certain terms with potential collaborators. Collaborations are complex and time consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

We may not be able to negotiate further collaborations on a timely basis, on acceptable terms, or at all. Even if we are able to obtain a license to intellectual property of interest, we may not be able to secure exclusive rights, in which case others could use the same rights and compete with us. Our existing collaboration partners may not prioritize our product candidates or otherwise not effectively pursue the development of our product candidates which may delay, reduce or terminate the development of such product candidate, reduce or delay its development program or delay its potential commercialization. Further if we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may have to delay, reduce or terminate the development of such product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. Doing so will likely harm our ability to execute our business plans. 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.

Risks Related to Intellectual Property

If we are unable to obtain, maintain and protect sufficient patent and other intellectual property rights for our product candidates and technology, or if the scope of patent and other intellectual property rights obtained is not sufficiently broad, we may not be able to compete effectively in our market.

Our success depends in significant part on our ability and the ability of future licensors, licensees or collaborators to obtain, maintain, enforce and defend patents and other intellectual property rights with respect to our product candidates and technology and to operate our business without infringing, misappropriating or otherwise violating the intellectual property rights of others. In the last year, we have filed multiple U.S. provisional applications covering methods of treatment and formulations of ETX-155. A U.S. provisional patent application is not eligible to become an issued patent until, among other things, we file non-provisional patent application within 12 months of filing of the provisional patent application. With regard to such U.S. provisional patent applications, if we do not timely file any non-provisional patent applications, we may lose our priority dates with respect to our provisional patent applications and any patent protection on the inventions disclosed in our provisional patent applications. While we intend to timely file non-provisional patent applications relating to our provisional patent applications, we cannot predict whether any such patent applications will result in the issuance of patents that provide us with any competitive advantage.

The patent prosecution process is expensive and time-consuming. We and our future licensors, licensees or collaborators may not be able to prepare, file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we or our future licensors will fail to identify patentable aspects of our research and development output in time to obtain patent protection or fail to file patent applications covering inventions made in the course of development and commercialization activities before a competitor or another third party files a patent application covering, or publishes information disclosing, a similar, independently-developed invention. Such competitor's or other third party's patent application may pose obstacles to our ability to obtain patent protection or limit the scope of the patent protection we may obtain.

Although we enter into non-disclosure and confidentiality agreements with parties who have access to confidential or patentable aspects of our research and development output, such as our employees, collaborators, CROs, CDMOs, consultants, advisors and other third parties, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. In addition, publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we or our future licensors were the first to make the inventions claimed in our owned or any future licensed patents or pending patent applications, or were the first to file for patent protection of such inventions.

The patent position of biotechnology and pharmaceutical companies generally is uncertain, involves complex legal and factual questions and is the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our and our current or future licensors' patent rights are uncertain. Our and our future licensors' pending, and future patent applications may not result in patents being issued that protect our technology or product candidates, in whole or in part, or which effectively exclude others from commercializing competitive technologies and product candidates. The patent examination process may require us or our future licensors to narrow the scope of the claims of our pending and future patent applications, and therefore, even if such patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us or otherwise provide us with any competitive advantage. Our and our licensors' patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until a patent issues from such applications, and then only to the extent the issued claims cover such technology. Any patents that we hold or in-license in the future may be challenged, narrowed, circumvented or invalidated by third parties. Consequently, we do not know whether any of our product candidates will be protectable or remain protected by valid and enforceable patents. Our competitors or other third parties may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner. Any of the foregoing could impair our competitive position and harm our business.

The patent protection we obtain for our product candidates and technologies may be challenged and rendered invalid and/or unenforceable.

Even if our owned patent applications issue as patents, the issuance of any such patents is not conclusive as to their inventorship, scope, validity or enforceability, and such patents may be challenged, invalidated, narrowed or held to be unenforceable, including in the courts or patent offices in the United States and abroad, or circumvented. We may be subject to a third-party preissuance submission of prior art to the United States Patent and Trademark Office (USPTO), or equivalent foreign bodies, or become involved in opposition, derivation, revocation, re-examination, post-grant and inter partes review or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. Moreover, we may have to participate in interference or derivation proceedings declared by the USPTO to determine priority or ownership of invention or in post-grant challenge proceedings, such as oppositions in a foreign patent office, that challenge priority of invention or other features of patentability. Such proceedings and any other patent challenges may result in loss of patent rights, loss of exclusivity, loss of priority or in patent claims being narrowed, invalidated or held unenforceable, which could limit our ability to stop others from using or commercializing similar or identical technology and products or limit the duration of the patent protection of our technology and product candidates. Such proceedings also may result in substantial cost and require significant time from our scientists and management, even if the eventual outcome is favorable to us. Moreover, there could be public announcements of the results of hearings, motions or other developments related to any of the foregoing proceedings. If securities analysts or investors perceive those results to be negative, it could cause the price of shares of our common stock to decline. Any of the foregoing could harm our business.

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we rely on third parties to develop and manufacture our product candidates, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with our collaborators, advisors, employees and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, such as trade secrets. Despite these contractual agreements with third parties, sharing trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor’s discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may harm our business.

In addition, these agreements typically restrict the ability of our advisors, employees, third-party contractors and consultants to publish data potentially relating to our trade secrets, although our agreements may contain certain limited publication rights. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of our agreements with third parties, independent development or publication of information by any of our third-party collaborators. A competitor’s discovery of our trade secrets would impair our competitive position and harm our business.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time-consuming and unsuccessful, and issued patents covering our technology and product candidates could be found invalid or unenforceable if challenged.

Competitors and other third parties may infringe, misappropriate or otherwise violate our issued patents or other intellectual property. In addition, our patents may become involved in inventorship or priority disputes. Our 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. To counter infringement or other unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents or that our patents are invalid or unenforceable. In a patent infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, in whole or in part, construe the patent’s claims narrowly or refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated, held unenforceable or interpreted narrowly. We may find it impractical or undesirable to enforce our intellectual property against some third parties.

In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, non-enablement or insufficient written description. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO or made a misleading statement during prosecution. Third parties may also raise similar claims before the USPTO or an equivalent foreign body, even outside the context of litigation. Potential proceedings include re-examination, post-grant review, inter partes review, interference proceedings, derivation proceedings and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). Such proceedings could result in the revocation of, cancellation of, or amendment to our patents in such a way that they no longer cover our technology or any product candidates that we may develop. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of the patent protection on the applicable product candidates or technology covered by the patent rendered invalid or unenforceable. Such a loss of patent protection would harm our business.

Interference or derivation proceedings provoked by third parties or brought by us or declared by the USPTO may be necessary to determine the ownership or priority of inventions with respect to our patents or patent applications. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Such licenses may not be available on commercially reasonable terms, or at all, or may be non-exclusive. If we are unable to obtain and maintain such licenses, we may need to cease the development, manufacture and commercialization of one or more of the product candidates we may develop. In addition, if we or any future licensors are unsuccessful in any inventorship disputes to which we or they are subject, we may lose valuable intellectual property rights, such as exclusive ownership of, or the exclusive right to use, our owned or any future in-licensed patents. The loss of exclusivity or the narrowing of such patent claims could limit our ability to stop others from using or commercializing similar or identical technology and products. Any of the foregoing could harm our business. Even if we are successful in any of the foregoing disputes, it could result in substantial costs and be a distraction to management and other employees. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation or proceeding.

Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Most of our competitors are larger than we are and have substantially greater resources. They are, therefore, likely to be able to sustain the costs of complex patent litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Accordingly, despite our efforts, we may not be able to prevent third parties from infringing, misappropriating or otherwise violating our intellectual property. Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims could result in substantial costs and diversion of management resources, which could harm our business. In addition, the uncertainties associated with litigation could compromise our ability to raise the funds necessary to continue our clinical trials, continue our internal research programs or in-license needed technology or other product candidates. There could also be public announcements of the results of the hearing, motions or other interim proceedings or developments. If securities analysts or investors perceive those results to be negative, it could cause the price of shares of our common stock to decline. Any of the foregoing events could harm our business.

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

Filing, prosecuting, maintaining, defending and enforcing patents and other intellectual property rights on our product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection or other intellectual property rights to develop their own products and may export otherwise infringing, misappropriating or violating products to territories where we have patent or other intellectual property protection, but enforcement rights are not as strong as those in the United States. These products may compete with our product candidates, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of some countries do not favor the enforcement of patents and other intellectual property rights, which could make it difficult for us to stop the infringement, misappropriation or other violation of our intellectual property rights generally. Proceedings to enforce our intellectual property rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful.

Many countries, including European Union countries, India, Japan and China, have compulsory licensing laws under which a patent owner may be compelled under specified circumstances to grant licenses to third parties. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In those countries, we may have limited remedies if patents are infringed or if we are compelled to grant a license to a third party, which could materially diminish the value of those patents. This could limit our potential revenue opportunities. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license, which could harm our business.

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

We cannot guarantee that any of our patent searches or analyses, including the identification of relevant patents, the scope of patent claims or the expiration of relevant patents, are complete or thorough, nor can we be certain that we have identified each and every third-party patent and pending patent application in the United States and abroad that is relevant to or necessary for the commercialization of our product candidates in any jurisdiction. For example, U.S. patent applications filed before November 29, 2000 and certain U.S. patent applications filed after that date that will not be filed outside the United States remain confidential until patents issue. Patent applications in the United States and elsewhere are published approximately 18 months after the earliest filing for which priority is claimed, with such earliest filing date being commonly referred to as the priority date. Therefore, patent applications covering our product candidates could have been filed by third parties without our knowledge. Additionally, pending patent applications that have been published can, subject to certain limitations, be later amended in a manner that could cover our product candidates or the use of our product candidates. The scope of a patent claim is determined by an interpretation of the law, the written disclosure in a patent and the patent's prosecution history. Our interpretation of the relevance or the scope of a patent or a pending application may be incorrect, which may negatively impact our ability to market our product candidates. We may incorrectly determine that our product candidates are not covered by a third-party patent or may incorrectly predict whether a third party's pending application will issue with claims of relevant scope. Our determination of the expiration date of any patent in the United States or abroad that we consider relevant may be incorrect, which may negatively impact our ability to develop and market our product candidates. Our failure to identify and correctly interpret relevant patents may negatively impact our ability to develop and market our product candidates.

If we fail to identify and correctly interpret relevant patents or if we are unable to obtain licenses to relevant patents, we may be subject to infringement claims. We cannot guarantee that we will be able to successfully settle or otherwise resolve such infringement claims. If we fail in any such dispute, in addition to being forced to pay damages, which may be significant, we may be temporarily or permanently prohibited from commercializing any of our product candidates that are held to be infringing. We might, if possible, also be forced to redesign product candidates so that we no longer infringe the third-party intellectual property rights. Any of these events, even if we were ultimately to prevail, could require us to divert substantial financial and management resources that we would otherwise be able to devote to our business and could harm our business.

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

It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our products, in which case we would be required to obtain a license from these third parties. The licensing or acquisition of third-party intellectual property rights is a competitive area, and several more established companies may pursue strategies to license or acquire third-party intellectual property rights that we may consider attractive or necessary. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. If we are unable to license such technology, or if we are forced to license such technology, on unfavorable terms, our business could be harmed. If we are unable to obtain a necessary license, we may be unable to develop or commercialize the affected product candidates, which could harm our business, and the third parties owning such intellectual property rights could seek either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation. Even if we are able to obtain a license, it may be non-exclusive, thereby giving our competitors access to the same technologies licensed to us.

Moreover, some of our patents and patent applications in the future may be co-owned with third parties. If we are unable to obtain an exclusive license to any such co-owners' interest in such patents or patent applications, such co-owners may be able to license their rights to other third parties, including our competitors, who could market competing products and technology. In addition, we may need the cooperation of any such co-owners in order to enforce such patents against third parties, and such cooperation may not be provided to us.

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

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

Depending upon the timing, duration and conditions of any FDA marketing approval of our product candidates, one or more of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments, and one or more of our foreign patents may be eligible for patent term extension under similar legislation, for example, in the European Union. In the United States, the Hatch-Waxman Amendments permit a patent term extension of up to five years for a patent covering an approved product as compensation for effective patent term lost during product development and the FDA regulatory review process. However, there are no assurances that the FDA or any comparable foreign regulatory authority or national patent office will grant such extensions, in whole or in part. For example, we may not receive an extension if we fail to exercise due diligence during the testing phase or regulatory review process, fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Moreover, the length of the extension could be less than we request. Only one patent per approved product can be extended, the extension cannot extend the total patent term beyond 14 years from approval, and only those claims covering the approved drug, a method for using it or a method for manufacturing it may be extended. If we are unable to obtain patent term extension or the term of any such extension is less than we request, the period during which we can enforce our patent rights for the applicable product candidate will be shortened, and our competitors may obtain approval to market competing products sooner. As a result, our revenue from applicable products could be reduced.

Further, if this occurs, our competitors may take advantage of our investment in development and trials by referencing our clinical and preclinical data and launch their product earlier than might otherwise be the case, and our competitive position and business could be harmed.

Changes in patent law could diminish the value of our patents, thereby impairing our ability to protect our product candidates.

Obtaining and enforcing patents in the pharmaceutical industry is inherently uncertain, due in part to ongoing changes in the patent laws. Depending on decisions by Congress, the federal courts, and the USPTO and equivalent institutions in other jurisdictions, the laws and regulations governing patents, and interpretation thereof, could change in unpredictable ways that could weaken our ability to obtain new patents or to enforce existing or future patents. For example, 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. Therefore, there is increased uncertainty with regard to our ability to obtain patents in the future, as well as uncertainty with respect to the value of patents once obtained.

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. Assuming that other requirements for patentability are met, prior to March 2013, in the United States, the first to invent the claimed invention was entitled to the patent, while outside the United States, the first to file a patent application was entitled to the patent. After March 2013, under the Leahy-Smith America Invents Act, or the Leahy-Smith Act, enacted in September 2011, the United States transitioned to a first inventor to file system in which, assuming that other requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent on an invention regardless of whether a third party was the first to invent the claimed invention. The Leahy-Smith Act also includes a number of significant changes that affect the way patent applications are prosecuted and may also affect patent litigation. These include allowing third-party submission of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent by USPTO-administered post-grant proceedings, including post-grant review, inter partes review and derivation proceedings. The USPTO recently developed new regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, particularly the first inventor-to-file provisions. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could harm our business.

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 if we fail to comply with these requirements.

Periodic maintenance fees, renewal fees, annuity fees and various other government fees on any issued patents and applications are required to be paid to the USPTO and foreign patent agencies in several stages over the lifetime of a patent. In certain circumstances, we may rely on our future licensors to pay these fees. The USPTO and various foreign patent agencies also require compliance with a number of procedural, documentary, fee payment and other similar requirements during the patent application and prosecution process.

Noncompliance events that could result in abandonment or lapse of a patent or patent application include failure to respond to official communications within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. 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 irrevocable abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. If we or any future licensors or collaborators fail to maintain the patents and patent applications covering our product candidates, our competitors might be able to enter the market with similar or identical products or technology, which would harm our business.

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

Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing, misappropriating or otherwise violating the intellectual property and other proprietary rights of third parties. There is considerable intellectual property litigation in the biotechnology and pharmaceutical industries. We may become party to, or be threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our product candidates and technology, including re-examination, interference, post-grant review, inter partes review or derivation proceedings before the USPTO or an equivalent foreign body. Numerous U.S. and foreign issued patents and pending patent applications owned by third parties exist in the fields in which we are developing our product candidates. In the event that any of these patents were asserted against us, we believe that we would have defenses against any such action, including that such patents are not valid or that we would be able to replace such technology with alternative, non-infringing technology. However, if any such patents were to be asserted against us and our defenses to such assertion were unsuccessful and such alternative technology was not available or technologically or commercially practical, unless we obtain a license to such patents, we could be liable for damages, which could be significant and include treble damages and attorneys' fees if we are found to willfully infringe such patents, and we could be precluded from commercializing any product candidates that were ultimately held to infringe such patents. Any potential future legal proceedings relating to these patents could cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. If we are unsuccessful in our challenges to these patents and become subject to litigation or are unable to obtain a license on commercially reasonable terms with respect to these patents, it could harm our business.

Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future, regardless of their merit. Even if we believe third-party intellectual property claims are without merit, there is no assurance that a court would find in our favor on questions of infringement, validity, enforceability or priority. A court of competent jurisdiction could hold that third-party patents asserted against us are valid, enforceable and infringed, which could adversely affect our ability to commercialize any product candidates we may develop and any other product candidates or technologies covered by the asserted third- party patents. In order to successfully challenge the validity of any such U.S. patent in federal court, we would need to overcome a presumption of validity. As this burden is a high one requiring us to present clear and convincing evidence as to the invalidity of any such U.S. patent claim, there is no assurance that a court of competent jurisdiction would invalidate the claims of any such U.S. patent. If we are found to infringe, misappropriate or otherwise violate a third party's intellectual property rights, and we are unsuccessful in demonstrating that such rights are invalid or unenforceable, we could be required to obtain a license from such a third party in order to continue developing and marketing our products and technology. 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, and it could require us to make substantial licensing and royalty payments. We could be forced, including by court order, to cease commercializing the infringing technology or product candidates. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties and other fees, redesign our infringing drug or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business. Any of the foregoing events would harm our business.

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

Many of our employees were previously employed at other biotechnology or pharmaceutical companies. Although we try to ensure that our employees, consultants and advisors 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 individuals have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's former employer. Litigation may be necessary to defend against these claims.

In addition, we or our future licensors may be subject to claims that former employees, collaborators or other third parties have an interest in our owned or any future in-licensed patents or other intellectual property as an inventor or co-inventor. While it is our policy to require our employees 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 conceives, develops or reduces to practice intellectual property that we regard as our own. Our and their assignment agreements may not be self-executing or may be breached, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property.

If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs, delay development of our product candidates and be a distraction to management. Any of the foregoing events would harm our business.

Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could compromise our ability to compete in the marketplace, including compromising our ability to raise the funds necessary to continue our clinical trials, continue our research programs, license necessary technology from third parties or enter into development collaborations that would help us commercialize our product candidates, if approved. Any of the foregoing events would harm our business.

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

We rely on trade secrets and confidentiality agreements to protect our unpatented know-how, technology and other proprietary information and to maintain our competitive position. Trade secrets and know-how can be difficult to protect. We seek to protect these trade secrets and other proprietary technology, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, collaborators, CROs, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. We cannot guarantee that we have entered into such agreements with each party that may have or has had access to our trade secrets or proprietary technology and processes. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third party, our competitive position would be harmed.

We may not be able to protect and enforce our trademarks and trade names, or build name recognition in our markets of interest thereby harming our competitive position.

We intend to rely on both registered and common law rights for our trademarks. We plan to apply to register these trademarks with the USPTO and may in the future seek to register additional trademarks in the United States and other countries. Our trademark applications may not be allowed for registration in a timely fashion or at all, and our future registered trademarks may not be maintained or enforced. In addition, any registered or unregistered trademarks or trade names that we own or will own may be challenged, infringed, circumvented, declared generic, lapsed or determined to be infringing on or dilutive of other marks. We may not be able to protect our rights in these trademarks and trade names or may be forced to stop using these names, which we need for name recognition by potential partners or customers in our markets of interest. In addition, third parties have filed, and may in the future file, for registration of trademarks similar or identical to our trademarks, thereby impeding our ability to build brand identity and possibly leading to market confusion. If they succeed in registering or developing common law rights in such trademarks, and if we are not successful in challenging such rights, we may not be able to use these trademarks to develop brand recognition of our technologies, products or services. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our registered or unregistered trademarks or trade names.

During the trademark registration process, we may receive Office Actions from the USPTO or from comparable agencies in foreign jurisdictions objecting to the registration of our trademark. Although we would be given an opportunity to respond to those objections, we may be unable to overcome such rejections. In addition, in the USPTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and/or to seek the cancellation of registered trademarks. Opposition or cancellation proceedings may in the future be filed against our trademark applications or registrations, and our trademark applications or registrations may not survive such proceedings. In addition, third parties may file first for our trademarks in certain countries. If they succeed in registering such trademarks, and if we are not successful in challenging such third-party rights, we may not be able to use these trademarks to market our products in those countries. If we do not secure registrations for our trademarks, we may encounter more difficulty in enforcing them against third parties than we otherwise would. If we are unable to establish name recognition based on our trademarks and trade names, we may not be able to compete effectively, which could harm our business.

Intellectual property rights do not necessarily address all potential threats.

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

- others may be able to make products that are similar to any product candidates we may develop or utilize similar technology but that are not covered by the claims of the patents that we own now or own or license in the future;
- we, or our future licensors, might not have been the first to make the inventions covered by the issued patent or pending patent application that we own now or own or license in the future;
- we, or our future licensors, might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;
- it is possible that our pending owned patent applications or those that we may own or license in the future will not lead to issued patents; issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors;
- our competitors might conduct research and development activities in the United States under FDA-related safe harbor patent infringement exemptions and/or in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- the patents of others may harm our business; and
- we may choose not to file a patent in order to maintain certain trade secrets or know-how, and a third party may subsequently file a patent covering such intellectual property.

Should any of these events occur, they could harm our business.

Risks Related to our Business Operations, Employee Matters and Managing Growth

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

We are highly dependent on the management, research and development, clinical, financial and business development expertise of our executive officers, as well as the other members of our scientific and clinical teams. Although we have employment offer letters with each of our executive officers, each of them may terminate their employment with us at any time. We do not maintain "key person" insurance for any of our executives or employees.

Recruiting and retaining qualified scientific and clinical personnel and, if we are successful in obtaining marketing approval for our product candidates, sales and marketing personnel, is critical to our success. The permanent or temporary loss of the services of our executive officers or other key employees for any reason could impede the achievement of our research, development and commercialization objectives, impair our operations and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval for and commercialize our product candidates. Competition to hire qualified personnel in our industry is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. Furthermore, to the extent we hire personnel from competitors, we may be subject to allegations that they have been improperly solicited or that they have divulged proprietary or other confidential information, or that their former employers own their research output. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited, and could harm our business.

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

Our full-time and part-time employee base grew from nine employees as of December 31, 2020 to 31 employees as of December 31, 2021. As our clinical development progresses, we expect to experience growth in the number of our employees and the scope of our operations, particularly in the areas of research, clinical operations, regulatory affairs, general and administrative and, if any of our product candidates receives marketing approval, sales, marketing and distribution. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

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

We are exposed to the risk that our employees, independent contractors, consultants, commercial collaborators, principal investigators, CROs and vendors may engage in fraudulent conduct or other illegal activity. Misconduct by these parties could include intentional, reckless or negligent conduct or unauthorized activities that violates (1) the laws and regulations of the FDA, the EMA, the MHRA and other similar regulatory authorities, including those laws requiring the reporting of true, complete and accurate information to such authorities, (2) manufacturing standards, (3) federal and state data privacy, security, fraud and abuse and other healthcare laws and regulations in the United States and abroad and (4) laws that require the true, complete and accurate reporting of financial information or data. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Misconduct by these parties could also involve the improper use of individually identifiable information, including information obtained in the course of clinical trials, creating fraudulent data in our preclinical studies or clinical trials or illegal misappropriation of product candidates, which could result in regulatory sanctions and harm our reputation.

We have adopted a code of business conduct and ethics, but it is not always possible to identify and deter misconduct by employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. Additionally, we are subject to the risk that a person or government could allege such fraud or other misconduct, even if none occurred. 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, including the imposition of significant civil, criminal and administrative penalties, including damages, fines, disgorgement, imprisonment, exclusion from participation in government healthcare programs, such as Medicare and Medicaid, contractual damages, reputational harm and the delay, reduction, termination or restructuring of our operations.

Our international operations in the United Kingdom may expose us to business, regulatory, political, operational, financial, pricing and reimbursement risks associated with doing business outside of the United States.

Our business is subject to risks associated with conducting business internationally. Some of our suppliers, industry partners and clinical study centers are located outside of the United States. Furthermore, our business strategy incorporates potential international expansion as we seek to obtain regulatory approval for, and commercialize, our product candidates in patient populations outside the United States. If approved, we may hire sales representatives and conduct physician and patient association outreach activities outside of the United States. Doing business internationally involves a number of risks, including but not limited to:

- multiple, conflicting and changing laws and regulations, including those related to Brexit related changes, such as privacy regulations, tax laws, export and import restrictions, employment laws, regulatory requirements, and other governmental approvals, permits and licenses;
- failure by us to obtain and maintain regulatory approvals for the use of our products in various countries; rejection or qualification of foreign clinical trial data by the competent authorities of other countries;
- delays or interruptions in the supply of clinical trial materials resulting from any events affecting raw material supply or manufacturing capabilities abroad, including those that may result from the ongoing COVID-19 pandemic;
- additional potentially relevant third-party patent and other intellectual property rights;
- complexities and difficulties in obtaining, maintaining, protecting and enforcing our intellectual property;
- difficulties in staffing and managing foreign operations;
- complexities associated with managing multiple payor reimbursement regimes, government payors or patient self-pay systems;
- limits in our ability to penetrate international markets;
- financial risks, such as longer payment cycles, difficulty collecting accounts receivable, the impact of local and regional financial crises on demand and payment for our product candidates and exposure to foreign currency exchange rate fluctuations;

- currency exchange rate fluctuations and the resulting effect on our revenue and expenses and the cost and risk of entering into hedging transactions if we chose to do so in the future;
- natural disasters, political and economic instability, including wars, terrorism and political unrest, outbreak of disease, including COVID-19 and related shelter-in-place orders, travel, social distancing and quarantine policies, boycotts, curtailment of trade and other business restrictions;
- certain expenses including, among others, expenses for travel and insurance; and
- regulatory and compliance risks that relate to anti-corruption compliance and record-keeping that may fall within the purview of the U.S. Foreign Corrupt Practices Act, its accounting provisions or its anti- bribery provisions or provisions of anti-corruption or anti-bribery laws in other countries.

Any of these factors could harm our future international expansion and operations and, consequently, our results of operations.

We may not be able to utilize a significant portion of our net operating loss carryforwards.

As of December 31, 2021, we had net operating loss carryforwards of approximately $6.0 million for federal income tax purposes, $16.5 million for foreign income tax purposes and $7.3 million for state income tax purposes. The federal net operating loss may be used up to 80% of future taxable income while the state and foreign losses may be used to offset up to 100% of future taxable income. The federal net operating loss carryforward can be carried forward indefinitely while the state net operating loss carryforward will begin to expire in varying amounts in 2039. The net operating loss carryforwards subject to expiration could expire unused and be unavailable to offset future income tax liabilities. Under the Tax Cuts and Jobs Act (Tax Act), as modified by the Coronavirus Aid, Relief and Economic Security Act (CARES Act), federal net operating losses incurred in taxable years beginning after December 31, 2017 and in future taxable years may be carried forward indefinitely, but the deductibility of such federal net operating losses in taxable years beginning after December 31, 2020 is limited.

Separately, under Section 382 of the Internal Revenue Code of 1986, as amended, (Internal Revenue Code), and corresponding provisions of state law, if a corporation undergoes an “ownership change,” which is generally defined as a greater than 50 percentage point change, by value, in its equity ownership by certain stockholders over a rolling three-year period, the corporation’s ability to use its pre-change NOL carryforwards and other pre-change tax attributes to offset its post-change income or taxes may be limited. The completion of our recent IPO, together with private placements and other transactions that have occurred since our inception, may trigger such an ownership change pursuant to Section 382 of the Internal Revenue Code. We have not completed a Section 382 analysis, and therefore, there can be no assurances that the NOLs carryforward are not already limited.

In addition, we may experience ownership changes as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. If an ownership change occurs and our ability to use our NOL carryforwards is materially limited, it could harm our future operating results by effectively increasing our future tax obligations.

We may seek to grow our business through acquisitions or investments in new or complementary businesses, products or technologies, through the licensing of products or technologies from third parties or other strategic alliances, and the failure to manage acquisitions, investments, licenses or other strategic alliances, or the failure to integrate them with our existing business, could have a material adverse effect on our operating results, dilute our stockholders’ ownership, increase our debt or cause us to incur significant expense.

Our success depends on our ability to continually enhance and broaden our product offerings in response to changing clinician and patients’ needs, competitive technologies and market pressures. Accordingly, from time to time we may consider opportunities to acquire, make investments in or license other technologies, products and businesses that may enhance our capabilities, complement our existing products and technologies or expand the breadth of our markets or customer base. Potential and completed acquisitions, strategic investments, licenses and other alliances involve numerous risks, including:

- difficulty assimilating or integrating acquired or licensed technologies, products, employees or business operations; issues maintaining uniform standards, procedures, controls and policies;
- unanticipated costs associated with acquisitions or strategic alliances, including the assumption of unknown or contingent liabilities and the incurrence of debt or future write-offs of intangible assets or goodwill;
- diversion of management’s attention from our core business and disruption of ongoing operations;

- adverse effects on existing business relationships with suppliers, sales agents, health care facilities, surgeons and other health care providers;
- risks associated with entering new markets in which we have limited or no experience;
- potential losses related to investments in other companies;
- potential loss of key employees of acquired businesses; and
- increased legal and accounting compliance costs.

We do not know if we will be able to identify acquisitions or strategic relationships we deem suitable, whether we will be able to successfully complete any such transactions on favorable terms, if at all, or whether we will be able to successfully integrate any acquired business, product or technology into our business or retain any key personnel, suppliers, sales agent, health care facilities, physicians or other health care providers. Our ability to successfully grow through strategic transactions depends upon our ability to identify, negotiate, complete and integrate suitable target businesses, technologies or products and to obtain any necessary financing. These efforts could be expensive and time-consuming and may disrupt our ongoing business and prevent management from focusing on our operations.

If we pursue any foreign acquisitions, they typically involve unique risks in addition to those mentioned above, including those related to integration of operations across different cultures, languages and legal and regulatory environments, currency risks and the particular economic, political and regulatory risks associated with specific countries.

To finance any acquisitions, investments or strategic alliances, we may choose to issue shares of our common stock as consideration, which could dilute the ownership of our stockholders. If the price of our common stock is low or volatile, we may be unable to consummate any acquisitions, investments or strategic alliances using our common stock as consideration. Additional funds may not be available on terms that are favorable to us, or at all.

Risks Related to our Common Stock

Our operating results may fluctuate significantly and may be difficult to predict.

Our quarterly and annual operating results may fluctuate significantly, due to a variety of factors, many of which are outside of our control and may be difficult to predict, including:

- the timing and cost of, and level of investment in, research, development and, if approved, commercialization activities relating to our product candidates, which may change from time to time;
- the timing and status of enrollment for our clinical trials;
- the cost of manufacturing our product candidates, as well as building out our supply chain, which may vary depending on the quantity of production and the terms of our agreements with manufacturers;
- expenditures that we may incur to acquire, develop or commercialize additional product candidates and technologies; timing and amount of any milestone, royalty or other payments due under any collaboration or license agreement; future accounting pronouncements or changes in our accounting policies;
- the timing and success or failure of preclinical studies and clinical trials for our product candidates or competing product candidates, or any other change in the competitive landscape of our industry, including consolidation among our competitors or partners;
- the timing of receipt of approvals for our product candidates from regulatory authorities in the United States and internationally; exchange rate fluctuations;
- coverage and reimbursement policies with respect to our product candidates, if approved, and potential future drugs that compete with our products; and
- the level of demand for our product candidates, if approved, which may vary significantly over time.

The trading price of the shares of our common stock may be volatile, and purchasers of our common stock could incur substantial losses.

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

- adverse regulatory decisions;
- any delay in our regulatory filings for our product candidates and any adverse development or perceived adverse development with respect to the applicable regulatory authority's review of such filings, including without limitation the FDA's issuance of a "refusal to file" letter or a request for additional information;
- the impact of the COVID-19 pandemic;
- the commencement, enrollment or results of any future clinical trials we may conduct, or changes in the development status of our product candidates;
- adverse results from, delays in or termination of our clinical trials or those of our competitors;
- unanticipated serious safety concerns related to the use of our product candidates;
- lower than expected market acceptance of our product candidates following approval for commercialization;
- changes in financial estimates by us or by any securities analysts who might cover our stock;
- conditions or trends in our industry;
- changes in the market valuations of similar companies;
- stock market price and volume fluctuations of comparable companies and, in particular, those that operate in the pharmaceutical industry;
- publication of research reports about us or our industry or positive or negative recommendations or withdrawal of research coverage by securities analysts;
- announcements by us or our competitors of significant acquisitions, strategic partnerships or divestitures;
- announcements of investigations or regulatory scrutiny of our operations or lawsuits filed against us;
- investors' general perception of our company and our business;
- recruitment or departure of key personnel;
- overall performance of the equity markets;
- trading volume of our common stock;
- disputes or other developments relating to intellectual property rights, including patents, litigation matters and our ability to obtain, maintain, defend, protect and enforce patent and other intellectual property rights for our technologies;
- significant lawsuits, including patent or stockholder litigation;
- proposed changes to healthcare laws in the United States or foreign jurisdictions, or speculation regarding such changes;
- general political and economic conditions; and
- other events or factors, many of which are beyond our control.

In the past, stockholders have initiated class action lawsuits against pharmaceutical and biotechnology companies following periods of volatility in the market prices of these companies' stock. Such litigation, if instituted against us, could cause us to incur substantial costs and divert management's attention and resources from our business.

A significant portion of our common stock may be sold into the market in the near future. This could cause the market price of our common stock to drop significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. If our stockholders sell, or the market perceives that our stockholders intend to sell, substantial amounts of our common stock in the public market, the market price of our common stock could decline significantly.

We have registered and intend to continue to register all shares of common stock that we may issue under our equity compensation plans. Once we register these shares, they can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates.

Additionally, the holders of an aggregate of 15.8 million shares of our common stock, or their transferees, have rights, subject to some conditions, to require us to file one or more registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. If we were to register the resale of these shares, they could be freely sold in the public market without limitation. If these additional shares are sold, or if it is perceived that they will be sold, in the public market, the trading price of our common stock could decline.

Anti-takeover provisions in our charter documents and under Delaware law could make an acquisition of our company more difficult, limit attempts by our stockholders to replace or remove our current management and limit the market price of our common stock.

Provisions in our amended and restated certificate of incorporation and amended and restated bylaws, as currently in effect, may have the effect of delaying or preventing a change of control or changes in our management. Our amended and restated certificate of incorporation and amended and restated bylaws include provisions that:

- provide for a classified board of directors whose members serve staggered terms;
- authorize our board of directors to issue, without further action by the stockholders, shares of undesignated preferred stock with terms, rights and preferences determined by our board of directors that may be senior to our common stock;
- require that any action to be taken by our stockholders be effected at a duly called annual or special meeting and not by written consent;
- specify that special meetings of our stockholders can be called only by our board of directors, the chairperson of our board of directors or our chief executive officer;
- establish an advance notice procedure for stockholder proposals to be brought before an annual meeting, including proposed nominations of persons for election to our board of directors;
- prohibit cumulative voting in the election of directors;
- provide that our directors may be removed for cause only upon the vote of the holders of at least 66 2/3% of our outstanding shares of common stock;
- provide that vacancies on our board of directors may be filled only by a majority of directors then in office, even though less than a quorum; and
- require the approval of our board of directors or the holders of at least 66 2/3% of our outstanding shares of common stock to amend our bylaws and certain provisions of our certificate of incorporation.

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, which is responsible for appointing the members of our management. In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law (DGCL), which generally, subject to certain exceptions, prohibits a Delaware corporation from engaging in any of a broad range of business combinations with any “interested” stockholder for a period of three years following the date on which the stockholder became an “interested” stockholder. Any delay or prevention of a change of control transaction or changes in our management could cause the market price of our common stock to decline.

Claims for indemnification by our directors and officers may reduce our available funds to satisfy successful third-party claims against us and may reduce the amount of money available to us.

Our amended and restated certificate of incorporation and amended and restated bylaws provide that we will indemnify our directors and officers, in each case to the fullest extent permitted by Delaware law.

In addition, as permitted by Section 145 of the DGCL, our amended and restated bylaws and our indemnification agreements that we have entered into with our directors and officers provide that:

- We will indemnify our directors and officers for serving us in those capacities or for serving other business enterprises at our request, to the fullest extent permitted by Delaware law. Delaware law provides that a corporation may indemnify such person if such person acted in good faith and in a manner such person reasonably believed to be in or not opposed to the best interests of the registrant and, with respect to any criminal proceeding, had no reasonable cause to believe such person's conduct was unlawful.
- We may, in our discretion, indemnify employees and agents in those circumstances where indemnification is permitted by applicable law.
- We are required to advance expenses, as incurred, to our directors and officers in connection with defending a proceeding, except that such directors or officers shall undertake to repay such advances if it is ultimately determined that such person is not entitled to indemnification.
- We will not be obligated pursuant to our amended and restated bylaws to indemnify a person with respect to proceedings initiated by that person against us or our other indemnitees, except with respect to proceedings authorized by our board of directors or brought to enforce a right to indemnification.
- The rights conferred in our amended and restated bylaws are not exclusive, and we are authorized to enter into indemnification agreements with our directors, officers, employees and agents and to obtain insurance to indemnify such persons.

We may not retroactively amend our amended and restated bylaw provisions to reduce our indemnification obligations to directors, officers, employees and agents.

Concentration of ownership of our common stock among our existing executive officers, directors and principal stockholders may prevent new investors from influencing significant corporate decisions and also reduces the public float for our common stock.

Based upon our common stock outstanding as of December 31, 2021, our executive officers, directors and current beneficial owners of 5% or more of our common stock, in the aggregate, beneficially own approximately 89.2% of our outstanding common stock. These stockholders, acting together, are able to significantly influence all matters requiring stockholder approval, including the election and removal of directors and any merger or other significant corporate transactions. The interests of this group of stockholders may not coincide with the interests of other stockholders.

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 the price at which shares were sold in the IPO 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.

In addition, as a result of this concentration of ownership, there is a limited number of number of shares of our common stock that are not held by officers, directors and controlling stockholders (which is referred to as our public float), thereby adversely impacting the liquidity of our common stock and potentially depressing the price at which you may be able to sell shares of common stock.

We have identified material weaknesses in our internal control over financial reporting. If we are unable to remediate these material weaknesses, or if we identify additional material weaknesses in the future or otherwise fail to maintain effective internal control over financial reporting, we may not be able to accurately or timely report our financial condition or results of operations, which may adversely affect our business.

Prior to the completion of the IPO, we were a private company with limited accounting personnel to adequately execute our accounting processes and other supervisory resources with which to address our internal control over financial reporting. In connection with the preparation of our consolidated financial statements, we identified material weaknesses in our internal control over financial reporting as of December 31, 2020 and December 31, 2021. A material weakness is a deficiency, or combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of the annual or interim consolidated financial statements will not be prevented or detected on a timely basis. The material weaknesses are as follows:

- We did not design or maintain an effective control environment. Specifically, we lacked a sufficient number of professionals with an appropriate level of accounting knowledge, training and experience to appropriately analyze, record and disclose accounting matters commensurate with accounting and reporting requirements. The lack of personnel contributed to additional material weaknesses.
- We did not design and maintain formal accounting policies, procedures and controls to achieve complete, accurate and timely financial accounting, reporting and disclosures, including segregation of duties and controls over the preparation and review of journal entries, account reconciliations and consolidation.

These material weaknesses did not result in a misstatement to the consolidated financial statements. However, these material weaknesses could result in a misstatement of our account balances or disclosures that would result in a material misstatement of our annual or interim consolidated financial statements that would not be prevented or detected.

- We did not design and maintain effective controls over information technology (IT) general controls for information systems that are relevant to the preparation of our consolidated financial statements. Specifically, we did not design and maintain (a) program change management controls to ensure that information technology program and data changes affecting financial IT applications and underlying accounting records are identified, tested, authorized and implemented appropriately, (b) user access controls to ensure appropriate segregation of duties and that adequately restrict user and privileged access to financial applications, programs, and data to appropriate personnel, (c) computer operations controls to ensure that critical batch jobs are monitored, and data backups are authorized and monitored, and (d) testing and approval controls for program development to ensure that new software development is aligned with business and IT requirements.

These IT deficiencies did not result in a misstatement to the consolidated financial statements. However, the IT deficiencies, when aggregated, could impact maintaining effective segregation of duties, as well as the effectiveness of IT-dependent controls (such as automated controls that address the risk of material misstatement to one or more assertions, along with the IT controls and underlying data that support the effectiveness of system-generated data and reports) that could result in misstatements potentially impacting all financial statement accounts and disclosures that would not be prevented or detected. Accordingly, management has determined the IT deficiencies in the aggregate constitute a material weakness.

We have implemented, and are continuing to implement, measures designed to improve internal control over financial reporting to remediate the control deficiencies that led to our material weaknesses by, among other things, hiring qualified personnel with appropriate expertise to perform specific functions and ensure adequate segregation of key duties and responsibilities, and designing and implementing improved policies, processes and internal controls, including ongoing senior management review and audit committee oversight. Further, we are implementing new financial systems to improve segregation of duties and controls and reliability of system generated data.

We are committed to continuing to improve our internal control processes and will continue to review, optimize and enhance our financial reporting controls and procedures. As we continue to evaluate and work to improve our internal control over financial reporting, we may take additional measures to address control deficiencies, or we may modify, or in appropriate circumstances not complete, certain of the remediation measures described above. These material weaknesses will not be considered remediated until the applicable controls operate for a sufficient period of time and management has concluded, through testing, that the enhanced control is operating effectively. We cannot assure you that the measures we have taken to date, and are continuing to implement, will be sufficient to remediate the material weaknesses we have identified or avoid potential future material weaknesses. If the steps we take do not correct the material weaknesses in a timely manner, we will be unable to conclude that we maintain effective internal controls over financial reporting. Accordingly, there could continue to be a reasonable possibility that these deficiencies or others could result in a misstatement of our accounts or disclosures that would result in a material misstatement of our consolidated financial statements that would not be prevented or detected on a timely basis.

As a public company, we are subject to additional requirements and regulations with respect to our accounting procedures and internal controls, which make it more difficult and costly for us to produce timely and accurate financial statements.

Following the closing of the IPO, we became subject to the reporting requirements of the Securities Exchange Act of 1934, as amended (Exchange Act), the Sarbanes-Oxley Act and the rules and regulations of the Nasdaq Stock Market. Section 302 of the Sarbanes-Oxley Act requires, among other things, that we report on the effectiveness of our disclosure controls and procedures in our quarterly and annual reports and, beginning with our annual report for the year ending 2022, Section 404 of the Sarbanes-Oxley Act requires that we perform system and process evaluation and testing of our internal control over financial reporting to allow management to report on the effectiveness of our internal control over financial reporting in our Form 10-K filing for that year. This requires that we incur substantial additional professional fees and internal costs to expand our accounting and finance functions and that we expend significant management efforts. Prior to the IPO, we were not required to test our internal control within a specified period, and, as a result, we may experience difficulty in meeting these reporting requirements in a timely manner going forward. In addition, our independent registered public accounting firm will be required to attest to the effectiveness of our internal control over financial reporting in our first annual report required to be filed with the SEC following the date we are no longer an emerging growth company or a smaller reporting company with less than $100 million in revenue.

If we are not able to comply with the requirements of Section 404 of the Sarbanes-Oxley Act 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 market price of our stock could decline and we could be subject to sanctions or investigations by the Nasdaq Stock Market, the SEC or other regulatory authorities. In addition, our common stock may not be able to remain listed on the Nasdaq Stock Market or any other securities exchange.

Our amended and restated certificate of incorporation designates the Court of Chancery of the State of Delaware and, to the extent enforceable, the federal district courts of the United States of America as the exclusive forums for substantially all disputes between us and our stockholders, which restricts our stockholders' ability to choose the judicial forum for disputes with us or our directors, officers, or employees.

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for the following types of claims or causes of action under Delaware statutory or common law: any derivative claims or causes of action brought on our behalf; any claims or causes of action asserting a breach of a fiduciary duty; any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, our amended and restated certificate of incorporation, or our amended and restated bylaws; or any action asserting a claim against us that is governed by the internal affairs doctrine. In addition, our amended and restated certificate of incorporation provides that the federal district courts of the United States of America will be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act. These choice of forum provisions will not apply to suits brought to enforce a duty or liability created by the Exchange Act or any other claim for which the federal courts have exclusive jurisdiction. Such provisions are intended to benefit and may be enforced by us, our officers and directors, employees and agents, including the underwriters for any offering giving rise to such complaint and any other professional or entity who has prepared or certified any part of the document underlying the offering and may result in increased costs for stockholders to bring a claim.

We believe these provisions may benefit us by providing increased consistency in the application of Delaware law and federal securities laws by chancellors and judges, as applicable, particularly experienced in resolving corporate disputes, efficient administration of cases on a more expedited schedule relative to other forums and protection against the burdens of multi-forum litigation. 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 lawsuits with respect to such claims or make such lawsuits more costly for stockholders, although our stockholders will not be deemed to have waived our compliance with federal securities laws and the rules and regulations thereunder. While the Delaware courts have determined that such choice of forum provisions are facially valid, a stockholder may nevertheless seek to bring a claim in a venue other than those designated in the exclusive forum provisions, and there can be no assurance that such provisions will be enforced by a court in those other jurisdictions. If a court were to find either choice of forum provision contained in our amended and restated certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions.

General Risk Factors

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

We expect our expenses to increase in connection with our planned operations. Unless and until we can generate a substantial amount of revenue from our product candidates, we expect to finance our future cash needs through public or private equity offerings, debt financings, collaborations, licensing arrangements or other sources, or any combination of the foregoing. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe that we have sufficient funds for our current or future operating plans.

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. In addition, debt financing, if available, may result in fixed payment obligations and may involve agreements that include restrictive covenants that limit our ability to take specific actions, such as incurring additional debt, making capital expenditures, creating liens, redeeming stock or declaring dividends, that could adversely impact our ability to conduct our business. 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.

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

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

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

We incur costs and demands upon our management as a result of complying with the laws and regulations affecting public companies in the United States, which may harm our business.

As a public company listed in the United States, we incur significant additional legal, accounting and other expenses. In addition, changing laws, regulations and standards relating to corporate governance and public disclosure, including regulations implemented by the SEC and the Nasdaq Stock Market, may increase legal and financial compliance costs and make some activities more time consuming. These laws, regulations and standards are subject to varying interpretations and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. We intend to invest resources to comply with evolving laws, regulations and standards, and this investment may result in increased general and administrative expenses and a diversion of management's time and attention from regular business activities to compliance activities. If, notwithstanding our efforts, we fail to comply with new laws, regulations and standards, regulatory authorities may initiate legal proceedings against us and our business may be harmed.

Failure to comply with these rules might also make it more difficult for us to obtain certain types of insurance, including director and officer liability insurance, and we might be forced to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. The impact of these events could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, on committees of our board of directors or as members of senior management.

If our information technology systems or data, or those of third parties upon which we rely, such as CROs, are or were compromised, we could experience adverse consequences resulting from such compromise, including but not limited to regulatory investigations or actions; litigation; fines and penalties; disruptions of our business operations; reputational harm; loss of revenue or profits; loss of customers or sales; and other adverse consequences.

In the ordinary course of our business, we may collect, store, use, transmit, disclose, or otherwise process proprietary, confidential, and sensitive data, including personal data (such as health-related data), intellectual property, and trade secrets. We may rely upon third parties service providers and technologies to operate critical business systems to process confidential information and personal data in a variety of contexts, including, without limitation, third-party providers of cloud-based infrastructure, encryption and authentication technology, employee email and other functions. Our ability to monitor these third parties' cybersecurity practices is limited, and these third parties may not have adequate information security measures in place. We may share or receive sensitive data with or from third parties.

Cyberattacks, malicious internet-based activity, and online and offline fraud are prevalent and continue to increase. These threats are becoming increasingly difficult to detect. These threats come from a variety of sources. In addition to traditional computer "hackers," threat actors, personnel (such as through theft or misuse), sophisticated nation-states, and nation-state-supported actors now engage in attacks.

We and the third parties upon which we rely, such as CROs, may be subject to a variety of evolving threats, including but not limited to social-engineering attacks (including through phishing attacks), malicious code (such as viruses and worms), malware (including as a result of advanced persistent threat intrusions), denial-of-service attacks (such as credential stuffing), personnel misconduct or error, ransomware attacks, supply-chain attacks, software bugs, server malfunctions, software or hardware failures, loss of data or other information technology assets, adware, telecommunications failures, geopolitical developments, earthquakes, fires, floods, and other similar threats. Ransomware attacks, including those perpetrated by organized criminal threat actors, nation-states, and nation-state-supported actors, are becoming increasingly prevalent and severe and can lead to significant interruptions in our operations, loss of data and income, reputational harm, and diversion of funds. For example, concerns have been raised about a potential increase in cybersecurity attacks generally as a result of the war between Russia and Ukraine and the resulting sanctions by U.S. and European governments, together with any additional future sanctions or other actions by them. Extortion payments may alleviate the negative impact of a ransomware attack, but we may be unwilling or unable to make such payments due to, for example, applicable laws or regulations prohibiting such payments. Similarly, supply-chain attacks have increased in frequency and severity, and we cannot guarantee that third parties and infrastructure in our supply chain or our third-party partners' supply chains have not been compromised or that they do not contain exploitable defects or bugs that could result in a breach of or disruption to our information technology systems (including our products and services) or the third-party information technology systems that support us and our services.

The COVID-19 pandemic and our remote workforce poses increased risks to our information technology systems and data, as more of our personnel work from home, utilizing network connections outside our premises. Future business transactions (such as acquisitions or integrations) could expose us to additional cybersecurity risks and vulnerabilities, as our systems could be negatively affected by vulnerabilities present in acquired or integrated entities' systems and technologies. Any of the previously identified or similar threats could cause a security incident or other interruption. A security incident or other interruption could result in unauthorized, unlawful, or accidental acquisition, modification, destruction, loss, alteration, encryption, disclosure of, or access to data. If such an event were to occur, it could result in a material disruption of our development programs and our business operations. For example, the loss of clinical trial data from completed, ongoing or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Likewise, we rely on third parties for the manufacture of our product candidates and to conduct clinical trials, and similar events relating to their computer systems could also harm our business. These threats pose a risk to the security of our systems, the confidentiality and the availability and integrity of our data, and these risks apply both to us, and to third parties on whose systems we rely for the conduct of our business.

We may expend significant resources or modify our business activities (including our clinical trial activities) in an effort to protect against security incidents. Certain data privacy and security obligations may require us to implement and maintain specific security measures, industry-standard or reasonable security measures to protect our information technology systems and data. While we have implemented security measures designed to protect against security incidents, there can be no assurance that these measures will be effective. We may be unable in the future to detect vulnerabilities in our information technology systems because such threats and techniques change frequently, are often sophisticated in nature, and may not be detected until after a security incident has occurred. Despite our efforts to identify and remediate vulnerabilities, if any, in our information technology systems, our efforts may not be successful. Further, we may experience delays in developing and deploying remedial measures designed to address any such identified vulnerabilities.

Applicable data privacy and security obligations may require us to notify relevant stakeholders of security incidents. Such disclosures are costly, and the disclosures or the failure to comply with such requirements could lead to adverse consequences. If we (or a third party upon whom we rely) experience a security incident or are perceived to have experienced a security incident, we may experience adverse consequences. These consequences may include: government enforcement actions (for example, investigations, fines, penalties, audits, and inspections); additional reporting requirements and/or oversight; restrictions on processing data (including personal data); litigation (including class claims); indemnification obligations; negative publicity; reputational harm; monetary expenditures; interruptions in our operations (including availability of data); financial loss; and other similar harms. Security incidents and attendant consequences may cause delays in the development of our product candidates and negatively impact our ability to grow and operate our business.

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

We are an "emerging growth company" and a "smaller reporting company," and as a result of the reduced reporting requirements applicable to "emerging growth companies" and "smaller reporting companies," our common stock may be less attractive to investors.

We are an "emerging growth company," as defined in the JOBS Act. For as long as we continue to be an "emerging growth company," we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not "emerging growth companies," including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved. We may take advantage of these exemptions until we are no longer an "emerging growth company." We could be an "emerging growth company" for up to five years, although circumstances could cause us to lose that status earlier, including if the aggregate market value of our common stock held by non-affiliates exceeds $700 million as of any June 30 (the end of our second fiscal quarter) before that time, in which case we would no longer be an "emerging growth company" as of the following December 31 (our fiscal year-end).

We are also a "smaller reporting company," as defined in the Exchange Act. 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 continue to take advantage of many of the same exemptions from disclosure requirements. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and the price of our common stock may be more volatile.

We may be unable to maintain adequate insurance coverage.

We presently have general liability, workers' compensation, directors' and officers' and product liability insurance coverage. Although we believe we will be able to maintain such coverage for a reasonable cost and obtain any additional coverages that our business may require, no assurances can be made that we will be able to do so.

Changes in tax laws or regulations that are applied adversely to us or our customers may seriously harm our business.

New income, sales, use or other tax laws, statutes, rules, regulations or ordinances could be enacted at any time, which could affect the tax treatment of any of our future domestic and foreign earnings. Any new taxes could adversely affect our domestic and international business operations, and our business and financial performance. Further, existing tax laws, statutes, rules, regulations or ordinances could be interpreted, changed, modified or applied adversely to us.

We have and expect to continue to rely on U.K. research and development tax credits and incentives as a source of capital for our business. The U.K. government is reviewing the requirements for this program and may change the eligibility criteria to receive such tax credits. In the event that the criteria are changed and we no longer qualify for these credits, we would lose a source of capital, which could harm our business.

Item 1B. Unresolved Staff Comments.

Not applicable.

Item 2. Properties.

We lease various operating spaces in the U.S. and the U.K. under non-cancelable operating lease arrangements that expire on various dates through January 31, 2025. As of December 31, 2021 and 2020, our future minimum lease payments under non-cancelable lease agreements were approximately $1.0 million and $47,000, respectively.

We believe that our existing facilities are adequate for the foreseeable future. As we expand, we believe that suitable additional alternative spaces will be available in the future on commercially reasonable terms, if required.

Item 3. Legal Proceedings.

As of the date of this Annual Report on Form 10-K, we are not party to any material legal matters or claims. We may become party to legal matters and claims arising in the ordinary course of business. We cannot predict the outcome of any such legal matters or claims, and despite the potential outcomes, the existence thereof may have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

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

Market Information

Our common stock has been listed on the Nasdaq Global Market under the symbol "ELYM" since August 10, 2021. Prior to that date, there was no public market for our common stock.

Holders of Common Stock

As of February 28, 2022, there were 26,567,681 shares of common stock issued and held by approximately 37 stockholders of record. The actual number of stockholders is greater than this number of record holders and includes stockholders who are beneficial owners but whose shares are held in street name by brokers and other nominees.

Securities Authorized for Issuance Under Equity Compensation Plans

Information about securities authorized for issuance under our equity compensation plans is incorporated herein by reference to Item 12 of Part III of this Annual Report on Form 10-K.

Dividend Policy

We have never declared or paid any cash dividends on our capital stock. We currently intend to retain all available funds and any future earnings to support our operations and finance the growth and development of our business. We do not intend to pay cash dividends on our common stock for the foreseeable future. Any future determination related to our dividend policy will be made at the discretion of our board of directors and will depend upon, among other factors, our results of operations, financial condition, capital requirements, contractual restrictions, business prospects and other factors our board of directors may deem relevant.

Recent Sales of Unregistered Securities.

The following sets forth information regarding all unregistered securities sold since January 1, 2021.

1. In March 2021, we issued an aggregate of 4,358,972 shares of our Series A-1 redeemable convertible preferred stock to five accredited investors at a purchase price of $7.80 per share, for an aggregate purchase price of approximately $34.0 million.
2. In May 2021, we issued an aggregate of 3,846,150 shares of our Series B redeemable convertible preferred stock to nine accredited investors at a purchase price of $15.60 per share, for an aggregate purchase price approximately $60.0 million.
3. From January 1, 2021 through August 12, 2021 (the date of filing our registration statement on Form S-8, File No. 333-258771), we granted to certain directors options to purchase an aggregate of 80,000 shares of our common stock under our 2021 Equity Incentive Plan at an exercise price of $12.50 per share.
4. From January 1, 2021 through July 16, 2021, we issued and sold an aggregate of 356,565 shares of our common stock pursuant to restricted stock purchase awards or upon the exercise of options under our 2019 Equity Incentive Plan or the Athenen Plan, at prices ranging from $0.0002 to $1.86 per share, for an aggregate exercise price of $109,505.
5. From January 1, 2021 through August 12, 2021 (the date of filing our registration statement on Form S-8, File No. 333-258771), we granted to certain employees, consultants, and directors options to purchase an aggregate of 2,310,335 shares of our common stock under our 2019 Equity Incentive Plan at exercise prices ranging from $0.0002 to $10.06 per share.

None of the foregoing transactions involved any underwriters, underwriting discounts or commissions, or any public offering. Unless otherwise specified above, we believe these transactions were exempt from registration under the Securities Act in reliance on Section 4(a)(2) of the Securities Act (and Regulation D promulgated thereunder), or Rule 701 promulgated under Section 3(b) of the Securities Act as transactions by an issuer not involving any public offering or under benefit plans and contracts relating to compensation as provided under Rule 701. The recipients of the securities in each of these transactions represented their intentions to acquire the securities for investment only and not with a view to or for sale in connection with any distribution thereof, and appropriate legends were placed on the share certificates issued in these transactions. All recipients had adequate access, through their relationships with us, to information about us. The sales of these securities were made without any general solicitation or advertising.

Use of Proceeds

On August 9, 2021 our Registration Statement on Form S-1, as amended (File No. 333-257980), was declared effective in connection with our IPO, pursuant to which we sold an aggregate of 7,360,000 shares of our common stock, including the full exercise of the underwriters' option to purchase additional shares, at a price to the public of $12.50 per share. Evercore L.L.C., Guggenheim Securities LLC, Stifel, Nicolaus & Company, Incorporated, and SVB Leerink LLC, acted as lead manager for the offering.

The IPO closed on August 12, 2021. The aggregate net proceeds from our IPO, after underwriting discounts and commissions of $6.4 million and other estimated offering expenses of $2.5 million, were $83.1 million. In connection with our IPO, no payments were made by us to directors, officers or persons owning ten percent or more of our common stock or to their associates or to our affiliates. There has been no material change in the planned use of proceeds from our IPO as described in our prospectus filed pursuant to Rule 424(b)(4) under the Securities Act with the SEC on August 11, 2021.

Issuer Purchases of Equity Securities

Not applicable.

Item 6. [Reserved]

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

You should read the following discussion and analysis together with our consolidated financial statements and related notes included in "Item 8. Financial Statements and Supplementary Data." in this Annual Report on Form 10-K. The following discussion contains forward-looking statements that involve risks and uncertainties. For a complete discussion of forward-looking statements, see the section above titled "Special Note Regarding Forward Looking Statements." Our actual results could differ materially from those expressed or implied in any forward-looking statements as a result of various factors, including those set forth under the caption "Item 1A. Risk Factors."

Overview

We are a clinical-stage biotechnology company focused on developing novel therapies for neuronal excitability disorders to address unmet needs in chronic pain, psychiatry, epilepsy and other disorders of the peripheral and central nervous systems. These disorders often occur when neurons are overly excited or inhibited, leading to an imbalance, and our focus is on restoring homeostasis. We are developing a pipeline of clinically differentiated product candidates focused on validated mechanisms of action with broad therapeutic potential to deliver improved therapeutics for patients with these disorders.

Our two lead clinical-stage candidates are ETX-810 and ETX-155. ETX-810 is a novel palmitoylethanolamide (PEA) prodrug initially being developed for the treatment of diabetic peripheral neuropathic pain (DPNP) and lumbosacral radicular pain (LSRP), commonly referred to as sciatica. ETX-810 is being evaluated in two Phase 2a clinical trials that are expected to report topline data in 2022 (DPNP Phase 2a in the first half of 2022, and LSRP Phase 2a in the second half of 2022). ETX-155 is a neurosteroid $GABA_A$ receptor positive allosteric modulator (PAM) initially being developed for the treatment of major depressive disorder (MDD), perimenopausal depression (PMD) and focal onset seizures (FOS), the most common type of seizure in people with epilepsy. In the first half of 2022, assuming FDA clearance of our IND filed in the first quarter of 2022, we plan to initiate two Phase 2a clinical trials for ETX-155 in patients with MDD and PMD, and we expect both to report topline data in the second half of 2023. In addition, we have initiated a Phase 1b proof-of-concept clinical trial in patients with photosensitive epilepsy that is expected to report interim data in the first half of 2022.

Below is a summary of our wholly owned pipeline.

Product Candidate (Mechanism)	Lead indications	Preclinical	Phase 1	Phase 2	Phase 3	Anticipated Clinical Milestones
ETX-810 (PEA prodrug)	Diabetic peripheral neuropathic pain					Topline Phase 2a data (1H 2022)
	Lumbosacral radicular pain (sciatica)					Topline Phase 2a data (2H 2022)
ETX-155 ($GABA_A$ receptor PAM)	Major depressive disorder (MDD)					Topline Phase 2a data (2H 2023)
	Perimenopausal depression (PMD)					Topline Phase 2a data (2H 2023)
	Focal onset seizure (FOS)					Phase 1b photosensitive epilepsy data (1H 2022)
Kv7 Program (Kv7.2/3 channel opener)	Pain, Epilepsy, Depression					
Next Gen Anxiolytic (2,3-benzo)	Generalized anxiety disorder (GAD)					

We have incurred significant operating losses since inception, as we have devoted substantially all of our resources to organizing and staffing our company, identifying potential product candidates, business planning, raising capital, undertaking research, executing preclinical studies and clinical development trials, and providing general and administrative support for business activities. We incurred net losses of $47.5 million and $20.7 million for the years ended December 31, 2021 and 2020, respectively. We had an accumulated deficit of $75.6 million and $28.1 million as of December 31, 2021 and December 31, 2020, respectively. Since our inception, we have funded our operations primarily with an aggregate of $208.3 million in net proceeds from the sale and issuance of shares of our redeemable convertible preferred stock and our initial public offering of our common stock. We had cash, cash equivalents, and marketable securities of $161.4 million and $20.5 million as of December 31, 2021 and December 31, 2020, respectively. Based on our current operating plan, we estimate that our cash, cash equivalents and marketable securities will be sufficient to fund our operating expenses and capital expenditure requirements into late 2023. We have based this estimate on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we expect.

We anticipate that our expenses and operating losses will increase substantially over the foreseeable future. The expected increase in expenses will be largely driven by our ongoing activities as we:

- continue to develop and conduct clinical trials, including for ETX-810 and ETX-155 for our initial and any potential additional indications; initiate and continue research and development, including preclinical, clinical and discovery efforts for any future product candidates; seek regulatory approvals for ETX-810 and ETX-155, or any other product candidates that successfully complete clinical development;
- add operational, financial and management information systems and personnel, including personnel to support our product candidate development and help us comply with our obligations as a public company;
- hire and retain additional personnel, such as clinical, manufacturing, quality control, scientific, commercial and administrative personnel; maintain, expand and protect our intellectual property portfolio;
- establish sales, marketing, distribution, manufacturing, supply chain and other commercial infrastructure in the future to commercialize various products for which we may obtain regulatory approval; and
- add equipment and physical infrastructure to support our research and development and growing staff; acquire or in-license other product candidates and technologies; and incur increased costs as a result of operating as a public company.

We do not have any products approved for sale and have not generated any revenue from product sales since our inception. Our ability to generate product revenue will depend on the successful development, regulatory approval and eventual commercialization of one or more of our product candidates, if approved. We cannot assure you that we will ever be profitable or generate positive cash flow from operating activities.

We will require substantial additional funding to support our continuing operations and further the development of our product candidates. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations through the sale of equity, debt financings or other capital sources, which could include income from collaborations, strategic partnerships or other strategic arrangements. To a lesser extent, we also expect to continue to rely on U.K. research and development tax credits and incentives for funding. Adequate funding may not be available when needed or on terms acceptable to us, or at all. If we are unable to raise additional capital as needed, we may have to significantly delay, scale back or discontinue development of our product candidates. Our ability to raise additional funds may be adversely impacted by potential worsening global economic conditions and the recent disruptions to, and volatility in, the credit and financial markets in the United States and worldwide, resulting from increased volatility in the trading prices for shares in the biopharmaceutical industry, the ongoing pandemic, or otherwise. In addition, our ability to continue to benefit from research and development tax credits and incentives will depend on our ability to continue meet the applicable requirements for them. If we fail to obtain necessary capital when needed on acceptable terms, or at all, it could force us to delay, limit, reduce or terminate our product development programs, commercialization efforts or other operations. Insufficient liquidity may also require us to relinquish rights to product candidates at an earlier stage of development or on less favorable terms than we would otherwise choose.

Acquisition

In October 2020, we acquired 100% of the share capital of Athenen Therapeutics, Inc. (the Athenen Acquisition), a company developing ETX-155, in a one-for-one exchange of their outstanding preferred and common stock. As a result, we issued a total of 2.5 million shares of Series A redeemable convertible preferred stock and 1.55 million shares of common stock, valued at $5.80 per share and $1.32 per share, respectively, for total purchase consideration of $16.5 million. The IPR&D acquired in this acquisition will enable us to continue to develop ETX-155. The Athenen Acquisition is accounted for as an asset acquisition. Since the acquired IPR&D did not have an alternative future use, we recognized a charge of $9.2 million which is included as a component of in-process research and development on the consolidated statements of operations and comprehensive loss for the year ended December 31, 2020.

Impact of the COVID-19 Pandemic on Our Operations

In March 2020, the World Health Organization characterized the outbreak of COVID-19 as a global pandemic and recommended containment and mitigation measures. Since then, extraordinary actions have been taken by international, federal, state, and local public health and governmental authorities to contain and combat the outbreak and spread of COVID-19 in regions throughout the world, including the U.K. and the State of Washington, where most of our operations are conducted. These actions substantially restricted daily activities for individuals and caused many businesses to curtail or cease normal operations. We have been carefully monitoring the COVID-19 pandemic as it continues to progress and its potential impact on our business. As a result of COVID-19, we have taken precautionary measures in order to minimize the risk of the virus to our employees, including the suspension of all non-essential business travel during peak periods of outbreak. In addition, all of our workforce has the ability to work remotely. To date, we have been able to continue our key business activities and advance our clinical programs. We have experienced delays in availability and shipping of preclinical and clinical supplies and delays in vendor services caused by understaffing or illness. However, to date, these delays have not materially impacted our business. However, in the future, it is possible that delays such as these or other disruptions such as delays related to enrolling participants in our clinical trials could impact our clinical development timelines. While the broader implications of the COVID-19 pandemic on our results of operations and overall financial performance remain uncertain, it has, to date, not had a material adverse impact on our results of operations or our ability to raise funds to sustain operations. The economic effects of the pandemic and resulting societal changes are currently not predictable, and the future financial impacts could vary from those foreseen.

Components of Operating Results

Operating Expenses

Our operating expenses consist of (i) research and development expenses, including expenses incurred with related parties, (ii) in-process research and development, and (iii) general and administrative expenses.

Research and Development

Our research and development expenses consist primarily of direct and indirect costs incurred in connection with our discovery efforts, preclinical studies, and clinical trial activities related to our pipeline, including our lead product candidates, ETX-810 and ETX-155.

Our direct research and development costs include:

- expenses incurred in connection with research, laboratory consumables and preclinical and clinical trial activities;
- the cost to manufacture drug products for use in our preclinical and clinical trials; and
- consulting fees, including services provided by a related party.

Our indirect research and development costs include:

- personnel-related expenses, such as salaries, bonuses, benefits, and stock-based compensation expense, for our scientific personnel performing research and development activities; and
- facility rent.

Total direct costs and indirect costs are as follows (in thousands):

	Year Ended December 31,	
	2021	2020
Direct costs	$ 25,166	$ 10,041
Indirect costs	4,752	1,730
Research and development tax credits	(6,596)	(2,429)
Total research and development expenses	$ 23,322	$ 9,342

We expense research and development costs as incurred. Non-refundable advance payments for goods and services that will be used over time for research and development are capitalized and recognized as goods are delivered or as the related services are performed. Costs to acquire technologies used in research and development that have not yet received regulatory approval and that are not expected to have an alternative future use are expensed when incurred. We categorize costs by stage of development clinical or preclinical. Given our stage of development and the utilization of our resources across our various programs, we have not historically tracked our research and development costs by program. Research and development expenses are presented net of reimbursement received for refundable research and development tax credits from the U.K. government.

Research and development costs by stage of development are as follows (in thousands):

	Year Ended December 31,	
	2021	2020
Clinical	$ 19,538	$ 7,179
Preclinical	10,380	4,592
Research and development tax credits	(6,596)	(2,429)
Total research and development expenses	$ 23,322	$ 9,342

Research and development activities are central to our business model. We expect our research and development expenses to increase substantially for the foreseeable future as we continue to ramp up our clinical development activities and incur expenses associated with hiring additional personnel to support our research and development efforts. Our research and development expenses may vary significantly based on factors such as:

- the number and scope of clinical studies needed for regulatory approval;
- the number and scope of preclinical and IND-enabling studies;
- the phases of development of our product candidates;
- the progress and results of our research and development activities;
- the length of time required to enroll eligible subjects and initiate clinical trials;
- the number of subjects that participate in the clinical trials;
- potential additional safety monitoring requested by regulatory agencies;
- the duration of subject participation in the trials and follow-up;
- the cost and timing of manufacturing of our product candidates;
- the timing, receipt and terms of any marketing approvals from applicable regulatory authorities;
- the hiring and retention of research and development personnel;
- the degree to which we obtain, maintain, defend and enforce our intellectual property rights; and
- the extent to which we establish collaborations, strategic partnerships or other strategic arrangements and the performance of any related third parties.

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

Research and development expenses, related party included expense reimbursements paid to Carnot Pharma, LLC, a related party, of $1.3 million and $0.6 million for the years ended December 31, 2021 and 2020, respectively.

In-process Research and Development

Our IPR&D expense consists of the relative fair value of the assets acquired and consideration given in connection with the Athenen Acquisition. As the assets acquired were in the research and development phase and were determined to not have any alternative future use, it was expensed as in-process research and development.

General and Administrative

Our general and administrative expenses consist primarily of personnel-related expenses, such as salaries, bonuses, benefits, and stock-based compensation, for our personnel in executive, finance and accounting, human resources, business development and other administrative functions. Other significant general and administrative expenses include legal fees relating to intellectual property and corporate matters, professional fees for accounting, tax and consulting services, insurance costs, and travel expenses.

We expect that our general and administrative expenses will substantially increase for the foreseeable future as we continue to increase our general and administrative headcount to support our continued research and development activities and, if any product candidates receive marketing approval, commercialization activities, as well as to support our operations generally. We also expect to incur increased expenses associated with operating as a public company, including costs related to accounting, audit, legal, regulatory, and tax-related services associated with maintaining compliance with exchange listing and Securities and Exchange Commission (SEC) requirements, director and officer insurance costs, and investor and public relations costs.

Other Income (Expense)

Change in Fair Value of Redeemable Convertible Preferred Tranche Liability

Our redeemable convertible preferred stock tranche lability was accounted for at fair value at inception, with changes in the fair value recorded in earnings at each reporting period through settlement. Refer to Note 6 of the consolidated financial statements.

Foreign Currency Gain (Loss)

Our foreign currency gain (loss) primarily consists of foreign exchanges gains and losses resulting from remeasurement and foreign currency transactions between the British Pound and the U.S. Dollar.

Other Income, net

Our other income consists of interest income, accretion and amortization related to our investments.

Results of Operations

The following table summarizes our results of operations for the years ended December 31, 2021 and 2020 (dollars in thousands):

	Year Ended December 31,		Change	
	2021	2020	$	%
Operating expenses:				
Research and development	$ 22,046	$ 8,769	$ 13,277	151.4 %
Research and development, related party	1,276	573	703	122.7 %
In-process research and development	—	9,158	(9,158)	(100.0)%
General and administrative	12,350	2,425	9,925	409.3 %
Total operating expenses	35,672	20,925	14,747	70.5 %
Loss from operations	(35,672)	(20,925)	(14,747)	70.5 %
Other income (expense):				
Change in fair value of redeemable convertible preferred stock tranche liability	(11,718)	—	(11,718)	100.0 %
Foreign currency gain (loss)	(170)	257	(427)	(166.1)%
Other income, net	80	—	80	100.0 %
Total other income (expense)	(11,808)	257	(12,065)	(4,694.6)%
Net loss	$ (47,480)	$ (20,668)	$ (26,812)	129.7 %

Comparison of the Years Ended December 31, 2021 and December 31, 2020

Operating Expenses

The following table sets forth our operating expenses (dollars in thousands):

	Year Ended December 31,		Change	
	2021	2020	$	%
Research and development	$ 22,046	$ 8,769	13,277	151.4 %
Research and development, related party	1,276	573	703	122.7 %
In-process research and development	—	9,158	(9,158)	(100.0)%
General and administrative	12,350	2,425	9,925	409.3 %
Total Operating Expenses	$ 35,672	$ 20,925	14,747	70.5 %

Research and Development and Research and Development, related party

Research and development expenses increased 151.4% from $8.8 million in 2020 to $22.0 million in 2021. Research and development expenses, related party increased 122.7% to $1.3 million in 2021. In total, research and development expenses increased 149.6% from $9.3 million in 2020 to $23.3 million in 2021. This increase was primarily driven by a $9.5 million increase in clinical expenses associated with Phase 1 and Phase 2 clinical trials of ETX-155 and ETX-810, a $5.8 million increase in preclinical expenses associated with ETX-155, ETX-810, and our preclinical programs, and a $2.9 million increase in personnel-related expenses from increased headcount and stock-based compensation. Clinical and preclinical costs have increased and are expected to continue to increase due to the further advancement of our programs into later stages of clinical development where clinical studies may have increased numbers of subjects, longer duration and more substantial data collection and analysis. The increase was partially offset by a $4.2 million increase in the refundable research and development tax credits from the U.K. generated from the increased research and development activities.

In-process Research and Development

In-process research and development expenses decreased by $9.2 million from 2020 to 2021 as the Athenen Acquisition was completed in October 2020, and we did not acquire any IPR&D in 2021.

General and Administrative

General and administrative expenses increased 409.3% from $2.4 million in 2020 to $12.4 million in 2021. The increase is primarily due to a $5.4 million increase in personnel-related expenses from increased headcount and stock-based compensation, as well as an increase of $3.1 million in consulting and legal expenses and an increase of $0.9 million in insurance costs.

Other Income (Expense)

The following table sets forth our other income (expense) (dollars in thousands):

	Year Ended December 31,		Change	
	2021	2020	$	%
Change in fair value of redeemable convertible preferred stock tranche liability	$ (11,718)	$ —	(11,718)	100.0 %
Foreign currency gain (loss)	(170)	257	(427)	(166.1)%
Other income, net	80	—	80	100.0 %
Total other income (expense)	$ (11,808)	$ 257	(12,065)	(4,694.6)%

Change in Fair Value of Redeemable Convertible Preferred Tranche Liability

For the year ended December 31, 2021, we recognized an $11.7 million charge from the remeasurement of our Series A-1 preferred stock tranche liability immediately prior to settlement.

Foreign Currency Gain (Loss)

Foreign currency gain (loss) decreased from a $0.3 million gain for the year ended December 31, 2020 to a $0.2 million loss for the year ended December 31, 2021. The loss was due to unfavorable foreign currency exchange rates between the British Pound and the U.S. Dollar.

Other Income, net

Other income, net increased by $0.1 million for the year ended December 31, 2021. The increase was due to the interest income, partially offset by amortization of premiums and accretion of discounts recognized on our investments recognized during the year. In 2020, we held no investments.

Liquidity and Capital Resources

Sources of Liquidity

We primarily generate cash and cash equivalents from the sale of our equity securities, including common stock and redeemable convertible preferred stock, and to a lesser extent from cash received pursuant to U.K. research and development tax credits and incentives. From our inception to December 31, 2021, we raised aggregate proceeds of $208.3 million from the issuance of shares of our redeemable convertible preferred stock and from our initial public offering of our common stock. We have not generated any revenue from product sales or otherwise. We have incurred net losses from operations since our inception and anticipate we will continue to incur net losses for the foreseeable future. As of December 31, 2021 and December 31, 2020, we had cash, cash equivalents, and marketable securities of $161.4 million and $20.5 million and an accumulated deficit of $75.6 million and $28.1 million, respectively.

Funding Requirements

We have experienced recurring net losses since inception. Our transition to profitability is dependent upon the successful development, approval and commercialization of our product candidates and achieving a level of revenue adequate to support our cost structure. We do not expect to achieve such revenue and expect to continue to incur losses for the foreseeable future. We believe our cash, cash equivalents, and marketable securities of $161.4 million as of December 31, 2021 will enable us to fund our operating expenses and capital expenditure requirements through late 2023.

We expect that our research and development and general and administrative expenses will continue to increase for the foreseeable future. As a result, we will need significant additional capital to fund our operations, which we may obtain through one or more equity offerings, debt financings or other third-party funding, including potential strategic alliances and licensing or collaboration arrangements. Because of the numerous risks and uncertainties associated with the development and commercialization of our product candidates, we are unable to estimate the amount of increased capital we will need to raise to support our operations and the outlays and operating expenditures necessary to complete the development of our product candidates and build additional manufacturing capacity, and we may use our available capital resources sooner than we currently expect.

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

- the progress of our current and future product candidates through preclinical and clinical development;
- potential delays in our preclinical studies and clinical trials, whether current or planned, or other factors;
- continuing our research and discovery activities;
- initiating and conducting additional preclinical, clinical, or other studies for our product candidates;
- changing or adding additional contract manufacturers or suppliers;
- seeking regulatory approvals and marketing authorizations for our product candidates;
- establishing sales, marketing, and distribution infrastructure to commercialize any products for which we obtain approval;
- acquiring or in-licensing product candidates, intellectual property and technologies;
- making milestone, royalty, or other payments due under any current or future collaboration or license agreements;

- obtaining, maintaining, expanding, protecting, and enforcing our intellectual property portfolio;
- potential delays or other issues related to our operations;
- meeting the requirements and demands of being a public company;
- defending against any product liability claims or other lawsuits related to our products; and
- the continued impact of the COVID-19 pandemic, which may exacerbate the magnitude of the factors discussed above.

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 sooner than currently projected, which 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 will need substantial additional funding to support our continuing operations and pursue our development strategy. Until such time as we can generate significant revenue from sales of our product candidates, 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 are unable 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 our product candidates or delay our efforts to expand our product pipeline. We may also be required to sell or license to other parties' rights to develop or commercialize our product candidates that we would prefer to retain.

Cash Flows

The following table summarized our cash flows (in thousands):

	Year Ended 'December 31,	
	2021	**2020**
Net cash used in operating activities	$ (36,072)	$ (14,098)
Net cash provided by (used in) investing activities	$ (114,970)	$ 8,078
Net cash provided by financing activities	$ 177,232	$ 4,925

Operating activities

In 2021, net cash used in operating activities was $36.1 million. This consisted primarily of net loss of $47.5 million and a net increase in our operating assets and liabilities of $4.2 million, primarily related to research and development activities, which was partially offset by the non-cash charges for changes in the fair value of the redeemable convertible preferred stock tranche liability of $11.7 million and stock-based compensation of $3.7 million.

In 2020, net cash used in operating activities was $14.1 million. This consisted primarily of net loss of $20.7 million and an increase in our operating assets and liabilities of $2.9 million, mostly related to research and development activities, which was partially offset by the non-cash charges for in-process research and development expenses of $9.2 million and stock-based compensation of $0.7 million

Investing activities

In 2021, net cash used in investing activities was $115.0 million. This consisted of purchases of investments in U.S. government debt securities, commercial paper, and corporate bonds.

In 2020, net cash provided by investing activities was $8.1 million, which was attributable to the $8.3 million in cash acquired from the Athenen Acquisition which was partially offset by the legal fees of $0.2 million paid for such acquisition

Financing activities

In 2021, net cash provided by financing activities was $177.2 million, primarily attributable to the proceeds, net of issuance costs, from the issuance of our Series A-1 and Series B redeemable convertible preferred stock, and the issuance of our common stock in our initial public offering.

In 2020, net cash provided by financing activities was $4.9 million, attributable to the proceeds, net of issuance costs, from the issuance of our Series A-1 redeemable convertible preferred stock.

Contractual Commitments and Obligations

In the normal course of business, we enter into contracts with contract research organizations (CROs), contract development and manufacturing organizations (CDMOs), and other third parties for preclinical studies and clinical trials, research and development supplies, and other testing and manufacturing services. These contracts do not contain material minimum purchase commitments and generally provide us the option to cancel, reschedule and adjust our requirements based on our business needs, prior to the delivery of goods or performance of services. However, it is not possible to predict the maximum potential amount of future payments under these agreements due to the conditional nature of our obligations and the unique facts and circumstances involved in each agreement.

We lease various operating spaces in the U.S. and the U.K. under non-cancelable operating lease arrangements that expire on various dates through January 31, 2025. As of December 31, 2021 and 2020, our future minimum lease payments under non-cancelable lease agreements were approximately $1.0 million and $47,000, respectively.

Off Balance Sheet Arrangements

We did not have any off-balance sheet arrangements as of December 31, 2021 and December 31, 2020.

Critical Accounting Policies and Estimates

A summary of the significant accounting policies is provided in Note 2 to our consolidated financial statements.

Our management's discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with U.S. GAAP. The preparation of 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 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.

Management considers an accounting estimate to be critical if:

- it requires a significant level of estimation uncertainty; and
- changes in the estimate are reasonably likely to have a material effect on our financial condition or results of operations.

We believe the following critical accounting policies and estimates describe the more significant judgments and estimates used in the preparation of our consolidated financial statements.

Stock-Based Compensation

We measure our stock-based awards granted to employees, non-employee directors, consultants and independent advisors based on the estimated grant-date fair value of the awards. We use the Black-Scholes option pricing model to estimate the fair value of our stock option awards. The Black-Scholes option pricing model requires us to make assumptions and judgements about the variables used in the calculation, including the fair value of common stock, expected term, expected volatility of our common stock, risk-free interest rate and expected dividend yield. Changes in the assumptions can materially affect the fair value and ultimately how much stock-based compensation is recognized. As a result, if factors or expected outcomes change and we use significantly different assumptions or estimates, our stock-based compensation recognized in future periods could be materially different.

Refer to Note 2 and 8 to our consolidated financial statements for further details regarding the development and evaluation of the assumptions used to estimate the fair value of our stock-based awards, and the related effect of stock-based compensation expense on the consolidated financial statements.

Fair Value of Common Stock

Following the closing of our IPO, the fair market value of our common stock is based on its closing price as reported on the date of grant on the Nasdaq Global Market, on which our common stock is traded. Prior to our IPO, because there was no public market for our common stock, the estimated fair value of our common stock was determined by the board of directors as of the date of each option grant with input from management, considering the most recently available third-party valuation of common stock, and the board of directors' assessment of additional objective and subjective factors that it believed were relevant and which may have changed from the date of the most recent valuation through the date of the grant.

The assumptions underlying these valuations represented management's best estimates which involved inherent uncertainties. As a result, if we had used significantly different assumptions or estimates, the fair value of our common stock and stock-based compensation expense could have been materially different.

Refer to Note 2 to our consolidated financial statements for further details regarding the factors considered and valuation approaches utilized in determining the best estimate of fair value of our common stock prior to our IPO.

Redeemable Convertible Preferred Stock Tranche Liability

Our Series A-1 redeemable convertible preferred stock included an obligation whereby the investors agreed to buy, and the Company agreed to sell, additional shares at a fixed price if certain agreed upon milestones were achieved (Series A-1 Tranche Rights). This redeemable convertible preferred stock tranche liability was determined to be a freestanding financial instrument that should be accounted for as a liability at fair value and was revalued at each reporting period until settlement, with changes in the fair value recorded as a change in redeemable convertible preferred stock tranche liability in the consolidated statements of operations and comprehensive loss. Upon the closing of the redeemable convertible preferred stock, the redeemable convertible preferred stock purchase rights liability was extinguished, and the mark-to-market fair value of the liability was included in the carrying value of the redeemable convertible preferred stock issued.

We estimated the fair value of the Series A-1 redeemable convertible preferred stock tranche liability using a probability-weighted present value model that considered the probability of triggering the Series A-1 Tranche Rights through achievement of the clinical development milestones specified in the Series A-1 redeemable convertible preferred stock purchase agreement. Significant estimates and assumptions impacting the fair value measurement included the estimated fair value per share of the underlying Series A-1 redeemable convertible preferred stock, risk-free rate, expected dividend yield, time to liquidity, expected volatility of the price of the underlying redeemable convertible preferred stock and determining the type of option (call option and/or forward contract) and associated probabilities. The most significant assumptions impacting the fair value of the redeemable convertible preferred stock tranche feature included the estimated fair value of our Series A-1 redeemable convertible preferred stock, estimated time to achieve the tranche milestone, and the determination of the type of option (call option and/or forward contract) and associated probability of success of completing the milestone.

We determined the estimated fair value per share of the underlying redeemable convertible preferred stock by taking into consideration the most recent sales of our redeemable convertible preferred stock as well as additional factors that we deemed relevant. We assessed these assumptions and estimates on a quarterly basis as additional information impacting the assumptions became available. The risk-free rate was determined by reference to the U.S. Treasury yield curve for time periods approximately equal to the expected term of the preferred stock tranche feature. We estimated a 0% dividend yield based on the expected dividend yield and the fact that we have never paid or declared dividends. We estimated the time to liquidity by weighting potential timelines associated with reaching various pipeline milestones. We historically have been a private company and lack company-specific historical and implied volatility information of our stock. Therefore, we estimated our expected stock volatility based on the historical volatility of a representative group of public companies in the biotechnology industry for the expected terms. The determination of the type of option is based on the payouts available to the holders of the Series A-1 Tranche Rights and the level of control the investors had over exercising these rights.

These estimates involved inherent uncertainties and the application of significant judgment. As a result, if factors or expected outcomes changed and we used significantly different assumptions or estimates, our redeemable convertible preferred stock tranche liability could have been materially different.

Internal Controls over Financial Reporting

In connection with the audit of our consolidated financial statements as of and for the years ended December 31, 2021 and 2020, we identified material weaknesses in our internal control over financial reporting. See the section titled "*Risk Factors—Risks Related to Our Common Stock —We have identified material weaknesses in our internal control over financial reporting. If we are unable to remediate the material weaknesses, or if we identify additional material weaknesses in the future or otherwise fail to maintain an effective system of internal controls, we may not be able to accurately or timely report our financial condition or results of operations, which may adversely affect our business*."

Emerging Growth Company Status

We are an emerging growth company, as defined in the Jumpstart Our Business Startups Act (JOBS Act). Under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards issued subsequent to the enactment of the JOBS Act until such time as those standards apply to private companies. Other exemptions and reduced reporting requirements under the JOBS Act for emerging growth companies include presentation of only two years audited consolidated financial statements in a registration statement for an initial public offering, an exemption from the requirement to provide an auditor's report on internal controls over financial reporting pursuant to the Sarbanes-Oxley Act, an exemption from any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation, and less extensive disclosure about our executive compensation arrangements. We have elected to use the extended transition period for complying with new or revised accounting standards that have different effective dates for public and private companies until the earlier of the date that (i) we are no longer an emerging growth company or (ii) we affirmatively and irrevocably opt out of the extended transition period provided in the JOBS Act.

As a result, our consolidated financial statements may not be comparable to companies that comply with the new or revised accounting pronouncements as of public company effective dates. We will remain an emerging growth company under the JOBS Act until the earliest of (i) the last day of our first fiscal year in which we have total annual gross revenue of $1.07 billion or more, (ii) the date on which we have issued more than $1.0 billion of non-convertible debt instruments during the previous three fiscal years, (iii) the date on which we are deemed a "large accelerated filer" under the rules of the SEC with at least $700.0 million of outstanding equity securities held by non-affiliates, or (iv) December 31, 2026.

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

As a smaller reporting company, we are not required to provide the information requested by this item pursuant to Item 305(e) of Regulation S-K.

Item 8. Financial Statements and Supplementary Data.

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

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

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Eliem Therapeutics, Inc. and its subsidiaries (the "Company") as of December 31, 2021 and 2020, and the related consolidated statements of operations and comprehensive loss, of redeemable convertible preferred stock and stockholders' equity (deficit) and of cash flows for the years then ended, including the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2021 and 2020, and the results of its operations and its cash flows for the years then ended in conformity with accounting principles generally accepted in the United States of America.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's consolidated financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits of these consolidated financial statements in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud.

Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ PricewaterhouseCoopers LLP
Seattle, Washington
March 7, 2022

We have served as the Company's auditor since 2021.

Eliem Therapeutics, Inc.
Consolidated Balance Sheets
(in thousands, except share and per share amounts)

	As of December 31,	
	2021	2020
Assets		
Cash	$ 46,922	$ 20,487
Short-term marketable securities	89,558	—
Prepaid expenses and other current assets	11,772	1,511
Total current assets	$ 148,252	$ 21,998
Long-term marketable securities	24,919	—
Other long-term assets	70	2,633
Total assets	$ 173,241	$ 24,631
Liabilities, redeemable convertible preferred stock, and stockholders' deficit		
Current liabilities:		
Accounts payable	$ 1,404	$ 1,086
Accounts payable, related party	—	207
Accrued expenses	4,588	1,219
Accrued expenses, related party	39	—
Redeemable convertible preferred stock tranche liability	—	551
Total current liabilities	$ 6,031	$ 3,063
Other long-term liabilities	7	—
Total liabilities	$ 6,038	$ 3,063
Commitments and contingencies (Note 7)		
Redeemable convertible preferred stock, $0.0001 par value per share, 10,000,000 and 12,909,389 shares authorized, 0 and 7,140,157 shares issued and outstanding with aggregate liquidation preference of $0 and $49,891 at December 31, 2021 and 2020, respectively	—	46,551
Stockholders' equity (deficit)		
Common stock, $0.0001 par value per share, 250,000,000 and 40,000,000 shares authorized and 26,235,317 and 3,418,751 shares issued and outstanding at December 31, 2021 and 2020, respectively	3	1
Additional paid-in capital	242,939	3,152
Accumulated other comprehensive loss	(123)	—
Accumulated deficit	(75,616)	(28,136)
Total stockholders' equity (deficit)	$ 167,203	$ (24,983)
Total liabilities, redeemable convertible preferred stock and stockholders' equity	$ 173,241	$ 24,631

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

Eliem Therapeutics, Inc.
Consolidated Statements of Operations and Comprehensive Loss
(in thousands, except share and per share amounts)

	Year Ended December 31,	
	2021	2020
Operating expenses:		
Research and development	$ 22,046	$ 8,769
Research and development, related party	1,276	573
In-process research and development	—	9,158
General and administrative	12,350	2,425
Total operating expenses	35,672	20,925
Loss from operations	(35,672)	(20,925)
Other income (expense):		
Change in fair value of redeemable convertible preferred stock tranche liability	(11,718)	—
Foreign currency gain (loss)	(170)	257
Other income, net	80	—
Total other income (expense)	(11,808)	257
Net loss	$ (47,480)	$ (20,668)
Accretion of redeemable convertible preferred stock to redemption value and cumulative preferred stock dividends	(4,548)	(2,285)
Net loss attributable to common stockholders	$ (52,028)	$ (22,953)
Net loss per share attributable to common stockholders, basic and diluted	$ (4.24)	$ (10.49)
Weighted-average shares used in computing net loss per share attributable to common stockholders, basic and diluted	12,260,551	2,187,813
Comprehensive loss:		
Net loss	$ (47,480)	$ (20,668)
Other comprehensive loss:		
Unrealized loss on investments, net of tax of $0	(123)	—
Comprehensive loss	$ (47,603)	$ (20,668)

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

Eliem Therapeutics, Inc.
Consolidated Statements of Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit)
(in thousands, except share and per share amounts)

	Redeemable Convertible Preferred Stock		Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount				
Balance as of December 31, 2019	3,999,133	$ 26,174	1,852,797	$ 1	$ 1,905	$ —	$ (7,468)	$ (5,562)
Issuance of Series A redeemable convertible preferred stock and common stock for the acquisition of in-process research and development from a related party	2,500,000	14,500	1,527,528	—	2,043	—	—	2,043
Issuance of Series A-1 redeemable convertible preferred stock, net of issuance costs of $75 and preferred stock tranche liability of $551	641,024	4,374	—	—	—	—	—	—
Accretion of redeemable convertible preferred stock	—	1,503	—	—	(1,503)	—	—	(1,503)
Vesting of restricted stock awards	—	—	38,426	—	—	—	—	—
Stock-based compensation	—	—	—	—	707	—	—	707
Net loss			—	—	—	—	(20,668)	(20,668)
Balance as of December 31, 2020	7,140,157	$ 46,551	3,418,751	$ 1	$ 3,152	$ —	$ (28,136)	$ (24,983)
Issuance of Series A-1 redeemable convertible preferred stock, net of issuance costs of $22	4,358,972	33,978	—	—	—	—	—	—
Reclassification of redeemable convertible preferred stock tranche liability upon settlement		12,269	—	—	—	—	—	—
Issuance of Series B redeemable convertible preferred stock, net of issuance costs of $39	3,846,150	59,961	—	—	—	—	—	—
Conversion of redeemable convertible preferred stock to common stock upon initial public offering	(15,345,279)	(152,759)	15,345,279	1	152,758	—	—	152,759
Proceeds from issuance of common stock in initial public offering, net of issuance costs of $8,856	—	—	7,360,000	1	83,143	—	—	83,144
Exercise of stock options and vesting of restricted stock awards	—	—	111,287	—	149	—	—	149
Stock-based compensation	—	—	—	—	3,737	—		3,737
Other comprehensive loss	—	—	—	—	—	(123)	—	(123)
Net loss	—	—	—	—	—	—	(47,480)	(47,480)
Balance as of December 31, 2021	—	$ —	26,235,317	$ 3	$ 242,939	$ (123)	$ (75,616)	$ 167,203

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

Eliem Therapeutics, Inc.
Consolidated Statements of Cash Flows
(in thousands)

	As of December 31,	
	2021	2020
Cash flows from operating activities		
Net loss	$ (47,480)	$ (20,668)
Adjustments to reconcile net loss to net cash used in operating activities:		
Stock-based compensation	3,737	707
Change in fair value of redeemable convertible preferred stock tranche liability	11,718	—
Investment amortization	370	—
Foreign currency gain from remeasurement	(245)	(359)
In-process research and development expenses	—	9,158
Changes in operating assets and liabilities:		
Prepaid expenses and other assets	(10,260)	(1,352)
Long-term assets	2,563	(2,524)
Accounts payable	318	(167)
Accrued liabilities	3,368	964
Accounts payable and accrued liabilities, related party	(168)	143
Long-term liabilities	7	—
Net cash used in operating activities	$ (36,072)	$ (14,098)
Cash flows from investing activities:		
Assets acquired in asset acquisition including cash	—	8,279
Cash used for purchase of in-process research and development from a related party	—	(201)
Purchase of marketable securities	(114,970)	—
Net cash provided by (used in) investing activities	$ (114,970)	$ 8,078
Cash flows from financing activities:		
Proceeds from initial public offering, net issuance costs	83,144	—
Proceeds from issuance of redeemable convertible preferred stock and related tranche rights, net of issuance costs	93,939	4,925
Proceeds from exercise of stock options	149	—
Net cash provided by financing activities	$ 177,232	$ 4,925
Effect of exchange rate changes on cash	245	359
Net change in cash and cash equivalents	$ 26,435	$ (736)
Cash and cash equivalents at beginning of period	20,487	21,223
Cash and cash equivalents at end of period	$ 46,922	$ 20,487
Supplemental disclosure of cash flow information:		
Conversion of redeemable convertible preferred stock to common stock	$ 152,759	$ —
Redeemable convertible preferred stock accretion	$ —	$ 1,503

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

Note 1. Nature of Operations and Basis of Presentation

Organization

Eliem Therapeutics, Inc. (the Company) is a clinical-stage biotechnology company focused on developing novel therapies for neuronal excitability disorders to address unmet needs in chronic pain, neuropsychiatry, epilepsy and other disorders of the peripheral and central nervous systems. Headquartered in Redmond, Washington, the Company was incorporated on October 18, 2018 as a Delaware corporation.

Basis of Presentation and Principles of Consolidation

The accompanying consolidated financial statements of the Company and its wholly owned subsidiaries have been prepared in conformity with accounting principles generally accepted in the United States (U.S. GAAP). All intercompany transactions and balances have been eliminated in consolidation.

Reverse Stock Split

In July 2021, the Company's board of directors approved an amendment to the Company's certificate of incorporation to effect a reverse split of shares of the Company's common stock on a 1-for-2 basis, which was effected on July 29, 2021 (the Reverse Stock Split). The number of authorized shares and the par values of the common stock were not adjusted as a result of the Reverse Stock Split. In connection with the Reverse Stock Split, the number of authorized shares, outstanding shares, and the conversion ratio for the Company's redeemable convertible preferred stock was proportionately adjusted such that the common stock issuable upon conversion of such preferred stock was decreased in proportion to the Reverse Stock Split. All references to common stock and options to purchase common stock share data, per share data, and related information contained in the consolidated financial statements have been retroactively adjusted to reflect the effect of the Reverse Stock Split for all periods presented.

Initial Public Offering

On August 12, 2021, the Company completed its initial public offering (IPO) of 7,360,000 shares of common stock, including the underwriters' full exercise of their over-allotment option at the IPO price of $12.50 per share. Gross proceeds from the IPO were $92.0 million, and the net proceeds were $83.1 million, after deducting underwriting discounts of $6.4 million and $2.5 million of offering costs payable by the Company. At the closing of the IPO, all of the Company's then outstanding redeemable convertible preferred stock was automatically converted into an aggregate of 15,345,279 shares of common stock. The related carrying value of the redeemable convertible preferred stock of $152.8 million was reclassified to common stock and additional paid-in capital.

Liquidity

Since inception, the Company has experienced recurring losses from operations and generated negative cash flows from operations. The Company has an accumulated deficit of $75.6 million and expects to incur additional losses from operations in the future. The Company estimates the available cash, cash equivalents, and marketable securities of $161.4 million as of December 31, 2021 will be sufficient to meet its projected operating requirements for at least the next twelve months from the filing date of these consolidated financial statements.

The Company will need to obtain substantial additional funding to develop and commercialize the Company's clinical programs as currently contemplated. The Company expects to finance future cash needs through equity offerings, debt financings, collaborations, strategic alliances, licensing arrangements and other marketing and distribution arrangements. In addition, the Company expects to continue to rely on capital markets, and to a lesser extent, U.K. research and development tax credits and incentives for funding. There are no assurances that the Company will be able to raise sufficient amounts of funding in the future on acceptable terms, or at all.

Note 2. Summary of Significant Accounting Policies

A summary of the significant accounting policies followed by the Company in the preparation of the accompanying consolidated financial statements follows:

Use of Estimates

The preparation of consolidated financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect reported amounts and disclosures. Accordingly, actual results could differ from those estimates. Estimates include those related to the valuation of assets acquired, accrual of research and development expenses, the valuation of stock-based awards, the valuation of common stock and redeemable convertible preferred stock, and the valuation of redeemable convertible preferred stock tranche liabilities. The Company evaluates its estimates and assumptions on an ongoing basis using historical experience and other factors and adjusts those estimates and assumptions when facts and circumstances dictate. Actual results could differ from those estimates.

Concentration of Credit Risk

Financial instruments that potentially subject the Company to concentrations of credit risk consist primarily of cash, cash equivalents, and marketable securities. The Company's cash is held by two financial institutions in the United States (U.S.) and two financial institutions in the United Kingdom (U.K.). The Company does not believe that it is subject to unusual credit risk beyond the normal credit risk associated with commercial banking relationships. The Company's deposits held in the U.S. and U.K. may exceed the Federal Depository Insurance Corporation and Financial Services Compensation Scheme, respectively, insured limits. The Company has investments in money market funds, U.S. government debt securities, commercial paper, and corporate bonds with high-quality accredited financial institutions.

Comprehensive Loss

Comprehensive loss consists of net loss and unrealized gains or losses on available-for-sale investments. The Company presents comprehensive loss and its components as part of the statements of operations and comprehensive loss.

Risks and Uncertainties

The Company is subject to risks and uncertainties common to early-stage companies in the biotechnology industry, including, but not limited to, development by competitors of new technological innovations, protection of proprietary technology, dependence on key personnel, reliance on single-source vendors and collaborators, availability of raw materials, patentability of the Company's products and processes and clinical efficacy and safety of the Company's products under development, compliance with government regulations and the need to obtain additional financing to fund operations. Product candidates currently under development will require significant additional research and development efforts, including extensive preclinical studies, clinical trials, and regulatory approval, prior to commercialization. These efforts will require significant amounts of additional capital, adequate personnel infrastructure and extensive compliance and reporting.

There can be no assurance that the Company's research and development will be successfully completed, that adequate protection for the Company's intellectual property will be obtained or maintained, that any products developed will obtain necessary government regulatory approval or that any approved products will be commercially viable. Even if the Company's product development efforts are successful, it is uncertain when, if ever, the Company will generate revenue from product sales. The Company operates in an environment of rapid technological change and substantial competition from other pharmaceutical and biotechnology companies. In addition, the Company is dependent upon the services of its employees, consultants and other third parties.

Moreover, the current COVID-19 pandemic, which is impacting worldwide economic activity, poses risk that the Company or its employees, contractors, suppliers, and other partners may be prevented from conducting business activities for an indefinite period of time which may increase costs and could delay the start-up and conduct of the Company's clinical trials, and negatively impact manufacturing and testing activities performed by third parties. Any significant delays and higher costs may impact the use and sufficiency of the Company's existing cash reserves, and the Company may be required to raise additional capital earlier than it had previously planned. The Company may be unable to raise additional capital if and when needed, which may result in delays or suspension of its development plans. The extent to which the pandemic will impact the Company's business will depend on future developments that are highly uncertain and cannot be predicted at this time.

Segments

Operating segments are identified as components of an enterprise about which separate discrete financial information is available for evaluation by the chief operating decision-maker (the CODM). The Company's CODM is its chief executive officer who reviews financial information together with certain operating metrics principally to make decisions about how to allocate resources and to measure the Company's performance. Management has determined that the Company operates as a single operating and reportable segment. The Company's CODM evaluates financial information on a consolidated basis. As the Company operates as one operating segment, all required segment financial information is found in the consolidated financial statements.

Fair Value Measurement

Assets and liabilities recorded at fair value on a recurring basis in the balance sheet are categorized based upon the level of judgment associated with the inputs used to measure their fair values. Fair value is defined as the exchange price that would be received for an asset or an exit price that would be paid to transfer a liability in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. The Company measures fair value based on a three-tier hierarchy, which prioritizes the inputs used in the valuation methodologies in measuring fair value as follows:

Level 1—Observable inputs such as unadjusted, quoted prices in active markets for identical assets or liabilities at the measurement date.

Level 2—Inputs (other than quoted prices included in Level 1) are either directly or indirectly observable for the assets or liabilities. These include quoted prices for similar assets or liabilities in active markets and quoted prices for identical or similar assets or liabilities in markets that are not active.

Level 3—Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

In determining fair value, the Company utilizes quoted market prices, or valuation techniques that maximize the use of observable inputs and minimize the use of unobservable inputs to the extent possible as well as considers counterparty credit risk in its assessment of fair value.

There were no transfers into or out of Level 3 for any of the periods presented.

The following table identifies the Company's assets and liabilities that were measured at fair value (in thousands):

	December 31, 2021			
	Level 1	Level 2	Level 3	Balance
Assets:				
Cash equivalents:				
Money market funds	$ 30,557	$ —	$ —	$ 30,557
Marketable securities:				
U.S. government debt securities	3,979	—	—	3,979
Commercial paper	—	54,363	—	54,363
Corporate bonds	—	56,135	—	56,135
Total marketable securities	3,979	110,498	—	114,477
Total assets	$ 34,536	$ 110,498	$ —	$ 145,034

	December 31, 2020			
	Level 1	Level 2	Level 3	Balance
Liabilities:				
Redeemable convertible preferred stock tranche liability	$ —	$ —	$ 551	$ 551
Total liabilities	$ —	$ —	$ 551	$ 551

As discussed further in Note 6, the redeemable convertible preferred stock tranche liability was settled on March 9, 2021, and the fair value of the liability was remeasured immediately prior to settlement.

Cash and Cash Equivalents

The Company considers all highly liquid investments purchased with original maturities of three months or less from the purchase date to be cash equivalents. As of December 31, 2021, the Company's cash equivalents consisted of money market funds. There were no cash equivalents as of December 31, 2020.

Asset Acquisition

In accordance with the guidance in Topic 805, Business Combinations, in the Financial Accounting Standards Board's (FASB) Accounting Standards Codification (ASC), the Company evaluates acquisitions of assets and related liabilities and other similar transactions to assess whether or not the transaction should be accounted for as a business combination or asset acquisition by first applying a screen test to determine if substantially all of the fair value of the gross assets acquired is concentrated in a single identifiable asset or group of similar identifiable assets. If the screen test is met, the transaction is accounted for as an asset acquisition. If the screen test is not met, further determination is required as to whether or not the Company has acquired inputs and processes that have the ability to create outputs which would meet the requirements of a business.

The Company accounts for an asset acquisition by recognizing net assets based on the cost to the acquiring entity on a relative fair value basis, which includes transaction costs in addition to consideration given. Goodwill is not recognized in an asset acquisition; any excess consideration transferred over the fair value of the net assets acquired is allocated to the non-monetary identifiable assets and liabilities assumed based on relative fair values. In-process research and development acquired in an asset acquisition is expensed provided there is no alternative future use.

Investments in Marketable Securities

Marketable securities are classified as available-for-sale, primarily consisting of U.S. government debt securities, commercial paper, and corporate bonds, and are reported at fair value. Unrealized holding gains and losses are reflected as a separate component of stockholders' equity (deficit) in accumulated other comprehensive loss until realized. Realized gains and losses on the sale of these securities are recognized in other income, net. The cost of marketable securities sold is based on the specific identification method.

The Company periodically reviews its available-for-sale securities to assess for credit impairment. Some of the factors considered in assessing impairment include the extent to which the fair value is less than the amortized cost basis, adverse conditions related to the security, an industry or geographic area, changes to security rating or sector credit ratings, and other relevant market data.

Research and Development Expenses

Research and development expenses consist primarily of research and development services and, to a lesser extent, salaries, benefits, and other personnel-related costs, including stock-based compensation, professional service fees, and other related costs such as facility rent, partially offset by fully refundable U.K. research and development tax credits. The Company recognizes the benefit of refundable research and development tax credits as a reduction of research and development expenses when there is reasonable assurance that the amount claimed will be recovered.

Research and development expenses includes estimates of the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of actual costs. Management estimates accrued expenses as of each balance sheet date in the consolidated financial statements based on facts and circumstances known at that time. Examples of estimated accrued research and development expenses include those related to fees paid to:

- vendors in connection with preclinical development activities;
- contract research organizations (CROs) in connection with preclinical studies and clinical trials; and
- contract development and manufacturing organizations (CDMOs) in connection with the production of preclinical and clinical trial materials.

All research and development costs are expensed in the period incurred, based on the estimates of the services received and efforts expended considering a number of factors, including, progress towards completion of the research, development and manufacturing activities, invoicing to date under the contracts, communication from the CROs, CDMOs and other companies of any actual costs incurred during the period that have not yet been invoiced and the costs included in the contracts and purchase orders. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which advance payments are made or payments made to vendors will exceed the level of services provided and result in a prepayment of the expense.

General and Administrative Expenses

General and administrative expenses consist primarily of personnel-related expenses, such as salaries, bonuses, benefits, and stock-based compensation, for our personnel in executive, finance and accounting, human resources, business development and other administrative functions. Other significant general and administrative expenses include legal fees relating to intellectual property and corporate matters, professional fees for accounting, tax and consulting services, insurance costs, and travel expenses. General and administrative costs are expensed as incurred.

Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consist primarily of amounts due for refundable research and development tax credits from the U.K. government and operating expenses paid in advance.

Leases

The Company leases office space in the U.S. and the U.K. The Company analyzes leases at the inception of each agreement for classification as either an operating or capital lease. The terms in the Company's lease agreements include rent holidays and rent escalation clauses. The Company recognizes rent expense on a straight-line basis equal to the amount of total minimum lease payments over the noncancelable term of the operating leases and, accordingly, records the
difference between cash rent payments and the recognition of rent expense as an increase or decrease in deferred rent liability.

Accretion and Classification of Redeemable Convertible Preferred Stock

The redeemable convertible preferred stock is classified outside of stockholders’ equity (deficit) on the consolidated balance sheets because the holders of such shares have liquidation rights in the event of a deemed liquidation that, in certain situations, are not solely within the control of the Company and would require the redemption of the then-outstanding redeemable convertible preferred stock.

The holders of the Company’s redeemable convertible preferred stock had the option to redeem their shares beginning in October 2026. As a result, these shares were considered probable of becoming redeemable since the redemption option depends solely on the passage of time. The Company accreted changes in the redemption value over the period from the date of issuance to the earliest redemption date of October 2026. In October 2020, the Company amended the terms of its Certificate of Incorporation to remove the redemption option of their Series A and Series A-1 redeemable convertible preferred stock, which was accounted for as a modification, and the Company ceased accretion.

Upon completion of the IPO on August 12, 2021, all of the Company's then outstanding redeemable convertible preferred stock were converted on a 1-for-1 basis to shares of common stock. As of December 31, 2021, the Company had no redeemable convertible preferred stock outstanding.

Redeemable Convertible Preferred Stock Tranche Liability

The Company’s Series A-1 redeemable convertible preferred stock included tranche rights that were determined to be freestanding financial instruments that should be accounted for as a liability at fair value (Note 6). This redeemable convertible preferred stock tranche liability was revalued at each reporting period until settlement with changes in the fair value recorded as a change in redeemable convertible preferred stock tranche liability in the consolidated statements of operations and comprehensive loss. Upon the closing of the redeemable convertible preferred stock, the redeemable convertible preferred stock purchase rights liability was extinguished, and the mark-to-market fair value of the liability was included in the carrying value of the redeemable convertible preferred stock issued.

As discussed further in Note 6, the Series A-1 redeemable convertible preferred tranche liability was settled on March 9, 2021 with the achievement of milestones set forth in the Series A-1 stock purchase agreement.

Stock-Based Compensation

The Company measures its stock-based awards granted to employees, non-employee directors, consultants and independent advisors based on the estimated grant-date fair value of the awards. For awards with only service conditions, including stock options and restricted stock awards, compensation expense is recognized over the requisite service period using the straight-line method. For awards that include performance conditions, compensation expense is not recognized until the performance condition is probable to occur. The Company uses the Black-Scholes option pricing model to estimate the fair value of its stock option awards. The Black-Scholes option pricing model requires the Company to make assumptions and judgements about the variables used in the calculations, including the fair value of common stock, expected term, expected volatility of the Company's common stock, risk-free interest rate and expected dividend yield. As the stock-based compensation is based on awards ultimately expected to vest, it is reduced by forfeitures, which the Company accounts for as they occur.

Fair Value of Common Stock

Following the closing of the Company's IPO, the fair market value of the Company's common stock is based on its closing price as reported on the date of grant on the Nasdaq Global Market, on which the Company's common stock is traded.

Prior to the Company's IPO, because there was no public market for the Company's common stock, the estimated fair value of the Company's common stock was determined by the board of directors as of the date of each option grant with input from management, considering the most recently available third-party valuation of common stock, and the board of directors' assessment of additional objective and subjective factors that it believed were relevant and which may have changed from the date of the most recent valuation through the date of the grant. Management believes that the board of directors has the relevant experience and expertise to determine fair value of the common stock. Third-party valuations were performed in accordance with the guidance outlined in the American Institute of Certified Public Accountants' Accounting and Valuation Guide, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation*. Management has considered numerous factors in determining the best estimate of fair value of our common stock, including the following:

- valuations performed by independent third-party specialists;
- the Company's operating results, financial position, and capital resources;
- the Company's stage of development and material risks related to its business;
- the progress of the Company's research and development programs;
- business conditions and projects;
- the lack of marketability of the Company's common stock and its redeemable convertible preferred stock as a private company;
- the prices at which the Company sold shares of redeemable convertible preferred stock to outside investors in arms-length transactions;
- the rights, preferences, and privileges of the Company's redeemable convertible preferred stock relative to those of the Company's common stock;
- the analysis of IPOs and the market performance of similar companies in the biotechnology industry;
- the likelihood of achieving a liquidity event for securityholders, such as an initial public offering or a sale of the Company, given prevailing market conditions;
- the hiring of key personnel and the experience of management;
- trends and developments in the industry; and
- external market conditions affecting the life sciences and biotechnology industry sectors.

For valuations performed in the first and second quarter of 2021, in accordance with the Practice Aid, the Company determined that the Hybrid Method, was the most appropriate method for determining the fair value of its common stock based on its stage of development and other relevant factors.

The Hybrid Method is a combination of an Option Pricing Method (OPM) scenario and one or more scenarios using a Probability Weighted Expected Return Method (PWERM). The Hybrid Method estimates the probability-weighted value across multiple scenarios, and uses the OPM to estimate the allocation of value within one or more of those scenarios. Weighting allocations are assigned to the OPM and PWERM methods factoring possible future liquidity events. The Company applied the Hybrid Method when it considered both an IPO and trade sale scenarios.

The OPM uses option theory to value the various classes of a company's securities in light of their respective claims to the enterprise value. Total stockholders' deficit value is allocated to the various share classes based upon their respective claims on a series of call options with strike prices at various value levels depending upon the rights and preferences of each class. A Black-Scholes closed form option pricing model is employed in this analysis, with an option term assumption that is consistent with the expected time to a liquidity event and a volatility assumption based on the estimated stock price volatility of a peer group of comparable public companies over a similar term.

The PWERM values each class of equity based on an analysis of the range of potential future enterprise values of the company and the manner in which those values would accrue to the owners of the different classes of equity. This method involves estimating the overall value of the subject company under various liquidity event scenarios and allocating the value to the various share classes based on their respective claim on the proceeds as of the date of each event. These different scenarios typically include an initial public offering, an acquisition, or a liquidation of the business, each resulting in a different value. For each scenario, the future value of each share class is calculated and discounted to a present value. The results of each scenario are then probability weighted in order to arrive at an estimate of fair value for each share class as of a current date.

For valuations performed in 2020, in accordance with the Practice Aid, the Company determined that the OPM was the most appropriate method for determining the fair value of its common stock based on its stage of development and other relevant factors.

The assumptions underlying these valuations represented management's best estimates, which involved inherent uncertainties and the application of management's judgment. As a result, if the Company had used significantly different assumptions or estimates, the fair value of its common stock and stock-based compensation expense could have been materially different.

Income Taxes

Income taxes are accounted for using the asset and liability method. Deferred tax assets and liabilities are recognized for the future tax consequences attributable to differences between the financial statement carrying amounts or existing assets and liabilities and their respective tax bases. Deferred tax assets and liabilities are measured using the enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect on deferred tax assets and liabilities of a change in tax rates is recognized in income in the period of enactment. The Company assesses the likelihood that its deferred tax assets will be recovered from future taxable income and, to the extent it believes, based upon the weight of available evidence, that it is more likely than not that all or a portion of the deferred tax assets will not be realized, a valuation allowance is established through a charge to income tax expense. Potential for recovery of deferred tax assets is evaluated by estimating the future taxable profits expected and considering prudent and feasible tax planning strategies.

The Company recognizes the tax benefit from an uncertain tax position if it is more likely than not that the tax position will be sustained upon examination by the tax authorities, based on the merits of the position. The Company's policy is to recognize interest and penalties related to the underpayment of income taxes as a component of income tax expense or benefit. To date, there have been no interest or penalties charged in relation to the unrecognized tax benefits.

Foreign Currency

The Company's reporting currency is the U.S. dollar. The functional currency of the Company and its subsidiaries is the U.S. dollar. Monetary assets and liabilities resulting from transactions denominated in currencies other than the functional currency are remeasured in the functional currency at exchange rates prevailing at the balance sheet date, and income items and expenses are translated into U.S. dollars at the average exchange rate in effect during the period. Exchange gains and losses resulting from remeasurement and foreign currency transactions are included in the determination of net loss.

Net Loss Per Share

Basic net loss per share attributable to common stockholders is calculated by dividing the net loss attributable to common stockholders by the weighted-average number of shares of common stock outstanding during the period, adjusted for outstanding shares that are subject to repurchase.

Diluted net loss per share attributable to common stockholders is computed by giving effect to all potentially dilutive securities outstanding for the period using the treasury stock method or the if-converted method based on the nature of such securities. For periods in which the Company reports net losses, diluted net loss per common share attributable to common stockholders is the same as basic net loss per share attributable to common stockholders, because potentially dilutive common shares are not assumed to have been issued if their effect is anti-dilutive.

Prior to completion of the IPO on August 12, 2021 (at which time the Company's then outstanding redeemable convertible preferred stock were converted on a 1-for-1 basis to shares of common stock, thereby eliminating the cumulative preferred stock dividend), basic net loss per share attributable to common stockholders was computed using the two-class method required for multiple classes of common stock and participating securities based upon their respective rights to receive dividends as if all income for the period has been distributed. The two-class method requires loss available to common stockholders for the period to be allocated between common and participating securities based upon their respective rights to share in undistributed earnings as if all loss for the period had been distributed. The Company’s participating securities included the Company’s redeemable convertible preferred stock, as the holders are entitled to receive dividends on a *pari passu* basis in the event that a dividend was paid on common stock. The holders of redeemable convertible preferred stock do not have a contractual obligation to share in losses of the Company, and therefore during periods of loss there was no allocation required under the two-class method.

Emerging Growth Company Status

The Company is an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012 (JOBS Act). Under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards issued subsequent to the enactment of the JOBS Act until such time as those standards apply to private companies. The Company has elected to avail itself of this extended transition period for complying with new or revised accounting standards that have different effective dates for public and private companies until the earlier of the date that it (i) is no longer an emerging growth company or (ii) affirmatively and irrevocably opts out of the extended transition period provided in the JOBS Act. As a result, these consolidated financial statements may not be comparable to companies that comply with the new or revised accounting pronouncements as of public company effective dates.

Recently Adopted Accounting Pronouncements

In August 2018, the FASB issued Accounting Standards Update (ASU) 2018-15, Intangibles — Goodwill and Other — Internal-Use Software (Subtopic 350-40): *Customer’s Accounting for Implementation Costs Incurred in a Cloud Computing Arrangement That Is a Service Contract*. ASU 2018-15 requires customers in a cloud computing arrangement that is a service contract to follow the internal-use software guidance in Accounting Standards Codification (ASC) 350-402 to determine which implementation costs to capitalize as assets, and is effective for non-public companies for annual periods beginning after 15 December 2020, and interim periods in annual periods beginning after 15 December 2021. The Company adopted ASU 2018-05 on January 1, 2021, which did not have a material impact on the Company’s consolidated financial statements.

Recent Accounting Pronouncements Not Yet Adopted

In February 2016, the FASB issued ASU No. 2016-02, Leases (Topic 842), related to leases to increase transparency and comparability among organizations by requiring the recognition of right-of-use (ROU) assets obtained in exchange for lease liabilities on the balance sheet. Most prominent among the changes in the standard is the recognition of ROU assets and lease liabilities by lessees for those leases classified as operating leases. Under the standard, disclosures are required to meet the objective of enabling users of consolidated financial statements to assess the amount, timing, and uncertainty of cash flows arising from leases. The effective date of this update for nonpublic companies is for fiscal years beginning after December 15, 2021 and interim periods therein. The Company estimates that adoption will not have a material impact on its consolidated financial statements.

In June 2016, the FASB issued ASU No. 2016-13, Financial Instruments—Credit Losses (Topic 326): *Measurement of Credit Losses on Financial Instruments*. The standard changes how entities will measure credit losses for most financial assets, including accounts and notes receivables. The standard will replace today's "incurred loss" approach with an "expected loss" model, under which companies will recognize allowances based on expected rather than incurred losses. Entities will apply the standard's provisions as a cumulative-effect adjustment to retained earnings as of the beginning of the first reporting period in which the guidance is effective. The effective date of this update for non-public companies is for fiscal years beginning after December 15, 2022 and interim periods therein. The Company estimates that adoption will not have a material impact on its consolidated financial statements

In December 2019, the FASB issued ASU No. 2019-12, Income Taxes (Topic 740): *Simplifying the Accounting for Income Taxes*. The standard simplifies the accounting for income taxes by removing certain exceptions to the general principles in Topic 740 and also improves consistent application by clarifying and amending existing guidance. The effective date of this update for non-public companies is for fiscal years beginning after December 15, 2021 and interim periods within fiscal years beginning after December 15, 2022. The Company is assessing the impact of this guidance and is continuing to evaluate the impact on its consolidated financial statements.

In August 2020, the FASB issued ASU 2020-06, *Debt—Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging — Contracts in Entity's Own Equity (Subtopic 815-40)—Accounting For Convertible Instruments and Contracts in an Entity's Own Equity*. The standard simplifies accounting for convertible instruments by removing major separation models required under current GAAP. Consequently, more convertible debt instruments will be reported as a single liability instrument with no separate accounting for embedded conversion features. ASU 2020-06 removes certain settlement conditions that are required for equity contracts to qualify for the derivative scope exception, which will permit more equity contracts to qualify for it. The standard also simplifies the diluted net income per share calculation in certain areas. The effective date of this update for non-public companies is for fiscal years beginning after December 15, 2023, including interim periods therein. Early adoption is permitted for fiscal years beginning after December 15, 2020 and interim periods therein. The Company is currently evaluating the impact that this new guidance will have on its consolidated financial statements.

3. Investments

Investments consists of available-for-sale securities as follows (in thousands):

	December 31, 2021			
	Amortized Cost	Unrealized Gain	Unrealized Loss	Estimated Fair Value
Short-term marketable securities:				
Commercial paper	$ 54,363	$ —	$ (1)	$ 54,362
Corporate bonds	35,231	—	(35)	35,196
Total short-term marketable securities	89,594	—	(36)	89,558
Long-term marketable securities:				
U.S. government debt securities	3,996	—	(17)	3,979
Corporate bonds	21,010	—	(70)	20,940
Total long-term marketable securities	$ 25,006	$ —	$ (87)	$ 24,919

All the commercial paper, U.S. government debt securities, and corporate bonds designated as short-term marketable securities have a contractual maturity date that is equal to or less than one year from the respective balance sheet date. Those that are designated as long-term marketable securities have a contractual maturity date that is more than one year from the respective balance sheet date.

Accrued interest receivable is excluded from the amortized cost and estimated fair value of the Company's marketable securities. Accrued interest receivable of $0.5 million is presented separately within the prepaid expenses and other current assets line items in the Company's consolidated balance sheet as of December 31, 2021.

As of December 31, 2021, there were $60.1 million of corporate bonds and $4.0 million of commercial paper in a continual unrealized loss position for less than 12 months. There were no investments in a continual unrealized loss position for greater than twelve months.

Furthermore, the Company did not intend, nor was the Company more likely than not to be required, to sell its available-for-sale investments before the recovery of the amortized cost basis, which may be maturity. Based on the Company's assessment, it concluded that none of the available-for-sale investments held as of December 31, 2021 were considered to be other-than-temporarily impaired, as such, no impairment loss was recorded for the year ended December 31, 2021. There was no realized gain or loss on available-for-sale securities in the periods presented.

There were no investments as of December 31, 2020.

4. Certain Balance Sheet Accounts

Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consist of the following (in thousands):

	December 31, 2021	December 31, 2020
Recoverable research and development tax credits	$ 6,523	$ —
Prepaid research and development expenses	2,906	1,500
Prepaid expenses	1,491	—
Other assets	852	11
Total prepaid expenses and other current assets	$ 11,772	$ 1,511

Accrued Expenses

Accrued expenses consist of the following (in thousands):

	December 31 2021	December 31, 2020
Accrued payroll	$ 2,220	$ 592
Accrued research and development expenses	2,159	627
Other accrued expenses	248	—
Total accrued expenses	$ 4,627	$ 1,219

5. Redeemable Convertible Preferred Stock

Upon completion of the IPO on August 12, 2021, all of the Company’s then outstanding redeemable convertible preferred stock was converted into an aggregate of 15,345,279 shares of common stock. As of December 31, 2021, the Company had no redeemable convertible preferred stock outstanding.

As of December 31, 2020, the Company’s redeemable convertible preferred stock consisted of the following balance (in thousands, except share and per share amounts):

	As of December 31, 2020				
	Issue Price	Shares Authorized	Shares Issued and Outstanding	Carrying Value	Aggregate Liquidation Preference
Series A	$ 6.00	2,717,084	2,717,082	$ 17,074	$ 18,569
Series A (Athenen Acquisition)	$ 5.80	2,500,000	2,500,000	$ 14,500	$ 15,253
Series A-1	$ 7.80	7,692,305	1,923,075	$ 14,977	$ 16,069
Ending balance		12,909,389	7,140,157	$ 46,551	$ 49,891

In March 2021, Series A-1 preferred stockholders exercised their tranche rights in connection with milestone achievements related to Phase 1 clinical trial results of ETX-155. As a result, the Company issued an additional 4,358,972 shares of Series A-1 redeemable convertible preferred shares for gross proceeds of $34.0 million. Upon exercise of the tranche rights, the Company reclassified the $12.3 million in preferred stock tranche liability to Series A-1 redeemable convertible preferred stock on the consolidated balance sheet.

In May 2021, the Company issued 3,846,150 shares of Series B redeemable convertible preferred stock for gross proceeds of $60.0 million.

Prior to conversion, the holders of the Series A, Series A-1, and Series B redeemable convertible preferred stock had various rights, preferences, privileges, and restrictions, with respect to voting, dividends, liquidation, and conversion.

Liquidation

In the event of any liquidation event, either voluntarily or involuntary, the holders of the Series B redeemable convertible preferred stock were entitled to receive, out of the assets of the Company before any payment shall be made or any assets distributed to the holders of Series A and A-1 redeemable convertible preferred stock, the Series B redeemable convertible preferred stock liquidation preference of $15.60, adjusted for any stock splits, combinations, and reorganizations, plus all unpaid cumulative dividends on each such share. If upon the liquidation event, the assets distributed among the holders of the Series B redeemable convertible preferred stock were insufficient to permit the payment to such holders of the full liquidation preference for their shares, then the holders of shares of the Series B redeemable convertible preferred stock shared ratably in any distribution of the assets available for distribution in proportion to their respective amounts, which otherwise would have been payable in respect of the shares held by them upon such distribution if all amounts payable on or with respect to such shares were paid the full preferential amount.

After the payment to the holders of the Series B redeemable convertible preferred stock of the full preferential amount, the holders of the Series A and Series A-1 redeemable convertible preferred stock were entitled to receive, out of the assets of the Company, the applicable liquidation preference specified for each series of redeemable convertible preferred stock before any payment was made or any assets distributed to the holders of common stock. Liquidation preference was $6.00 for Series A and $7.80 for Series A-1, each adjusted for any stock splits, combinations, and reorganizations, plus all unpaid cumulative dividends on each such share. If upon the liquidation event, the assets distributed among the holders of the Series A and A-1 redeemable convertible preferred stock were insufficient to permit the payment to such holders of the full liquidation preference for their shares, then the holders of shares of the redeemable convertible preferred stock shared ratably in any distribution of the assets available for distribution in proportion to their respective amounts, which otherwise would have been payable in respect of the shares held by them upon such distribution if all amounts payable on or with respect to such shares were paid the full preferential amount.

After the payment to the holders of the redeemable convertible preferred stock of the full preferential amount specified above, any remaining assets of the Company would have been distributed pro rata among all holders of the preferred and common stock.

A liquidation event required approval by the holders of at least a majority of the outstanding shares of redeemable convertible preferred stock and at least 70% of the then outstanding shares of Series B redeemable convertible preferred stock.

Optional Conversion

Each share of redeemable convertible preferred stock was convertible into common stock at the stockholder’s option. The converted shares would have been determined by dividing the original issue price for each series by the applicable conversion price for such series in effect at the date of conversion. The conversion price for each share of redeemable convertible preferred stock was initially equal to the original issuance price applicable to such share, with the exception of the Series A redeemable convertible preferred stock issued related to the Athenen Acquisition, which were convertible at any time after the date of issuance into common stock at the original issue price of the original Series A of $6.00. The conversion ratio was subject to appropriate adjustments for anti-dilution provisions, including stock splits, stock dividends, subdivisions, combinations, recapitalization events or similar events.

Specific to the Series B redeemable convertible preferred stock, the conversion ratio was subject to specific anti-dilution provisions adjustments if there was common stock issued for consideration below the Series B issue price.

Automatic Conversion

Each share of redeemable convertible preferred stock was convertible into common stock at initial conversion rates described under the Optional Conversion heading above, subject to adjustments based on certain antidilution provisions, including stock splits, stock dividends, subdivision, combinations, recapitalization or similar events, as provided by the Company's certificate of incorporation. Further, all shares of redeemable convertible preferred stock automatically would have converted into common stock upon the vote or written consent of the holders of a majority of the shares of redeemable convertible preferred stock or upon the closing of a firm-commitment underwritten public offering of the Company's common stock at a stock price of at least $17.16 per share and with gross aggregate proceeds to the Company of at least $80.0 million.

Upon completion of the IPO, the Company's redeemable convertible preferred stock was converted into 15,345,279 shares of common stock.

Dividends

The holders of shares of Series A, Series A-1, and Series B redeemable convertible preferred stock were entitled to receive cumulative dividends of 8% per annum of the original issuance price on each share of redeemable convertible preferred stock. The dividends were payable in cash, out of the assets at the time legally available thereof, when, as and if declared by the Board of Directors, on an equal basis according to the number of shares of redeemable convertible preferred stock held by such holders, prior and in preference to the common stock. As of December 31, 2020, the Company had total dividends in arrears for the Series A redeemable convertible preferred stock of $2.5 million, or $0.48 per share, and for Series A-1 redeemable convertible preferred stock of $1.1 million, or $0.56 per share. As of December 31, 2021, the Company had no dividends in arrears as all shares of redeemable convertible preferred stock converted to common stock upon the completion of the IPO.

Redemption

Under certain circumstances, subsequent to the occurrence of a deemed liquidation event, defined as (1) a majority of the holders of the then outstanding redeemable convertible preferred stock and (2) at least 70% of the then outstanding shares of the Series B redeemable convertible preferred stock could have required the Company to redeem their shares at a price per share equal to the liquidation amount, to the extent that sufficient funds were available. Additionally, holders of the Company's Series A and Series A-1 redeemable convertible preferred stock initially had the option to redeem their shares beginning in October 2026. As a result, these shares were considered probable of becoming redeemable since redemption is solely dependent on the passage of time. As such, the Company adjusted the carrying value of the redeemable convertible preferred stock by accreting changes in the redemption value over the period from the date of issuance to the earliest redemption date of October 2026. In October 2020, the Company amended the terms of their Certificate of Incorporation to remove the redemption option of their Series A and Series A-1 redeemable convertible preferred stock, as a result the Company ceased recording adjustments to the carrying value of its outstanding redeemable convertible preferred stock for accretion to redemption value. There was no change in value as a result of this modification. There was no accretion to redemption value recorded for the year ended December 31, 2021.

Voting

The holders of the Company's Series B redeemable convertible preferred stock, voting together as a class, were entitled to elect one (1) member of the Board of Directors (the Series B director). The holders of the Company's Series A and Series A-1 redeemable convertible preferred stock, voting together as a class, were entitled to elect two (2) members of the Board of Directors (the Series A directors). The holders of the shares of common stock and of any other class or series of voting stock (including the preferred stock), voting together as a class, were entitled to elect the balance of the Company's directors.

Stockholder Rights

The holders of the Company's redeemable convertible preferred stock had protective provisions that required preferred stockholders representing a majority of the outstanding redeemable convertible preferred stock, voting as a single class (on an as-converted basis), to consent to specific actions including the following: changes in the corporation's certificate of incorporation or bylaws that would affect, alter or change the preference or rights of the redeemable convertible preferred stock, changes in the authorized number of shares, declaration or payment of dividends, repurchase of shares, changes in the size of the Board of directors, creation of a new class or series of stock, or taking any action that would cause a liquidation event.

Further, the holders of the Company's Series B redeemable convertible preferred stock had additional protective provisions that required Series B preferred stockholders representing 70% of the outstanding shares of the Series B redeemable convertible preferred stock to consent to specific actions including the following: changes in the corporation's certificate of incorporation or bylaws that would affect, alter or change the preference or rights of the Series B redeemable convertible preferred stock, changes in the authorized number of shares of Series B redeemable convertible preferred stock, declaration or payment of dividends or distributions shares of capital stock other than the Series A, Series A-1, and Series B redeemable convertible preferred stock, sell shares of Common Stock to the public at price below $17.16 in a firm-commitment underwritten public offering, or taking any action that would cause a liquidation event that would results in proceeds of less than $17.16 per share of the Series B redeemable convertible preferred stock.

Additionally, the holders of the Company's Series A and Series A-1 redeemable convertible preferred stock had additional protective provisions that required preferred stockholders representing a majority of the outstanding redeemable convertible preferred stock, voting as a single class (on an as-converted basis), to consent to specific actions including the following: changes in the corporation's certificate of incorporation or bylaws that would affect, alter or change the preference or rights of the Series A and Series A-1 redeemable convertible preferred stock and changes or reclassifications of any existing security of the Company that is pari passu with the Series A and/or Series A-1 redeemable convertible preferred stock.

6. Redeemable Convertible Preferred Stock Tranche Liability

The purchasers of Series A-1 redeemable convertible preferred stock also received tranche rights (Series A-1 Tranche Rights), which provided them the right to purchase additional shares of Series A-1 redeemable convertible preferred stock in a future tranche. This tranche was for the purchase of Series A-1 redeemable convertible preferred stock and was valued based upon the Company achieving certain future milestones and utilized a valuation model that reflected both potential outcomes of success or failure to meet the milestone.

Upon issuance in October 2020, the Series A-1 redeemable convertible preferred tranche liability was valued at $0.86 per share. There was no change in value from the date of issuance and December 31, 2020.

The Company estimated the fair value of the Series A-1 Tranche Rights using a probability-weighted present value model that considered the probability of triggering the Series A-1 Tranche Rights through achievement of the clinical development milestones specified in the Series A-1 purchase agreement. These estimates were based, in part, on subjective assumptions. Changes to these assumptions could have had a significant impact on the reported fair value of the Series A-1 Tranche Rights.

The following reflects the significant quantitative inputs used in the valuation of the redeemable convertible preferred stock tranche liability:

	Series A-1 Tranche Call Option
Estimated fair value of redeemable convertible preferred stock	$6.94 - $11.10
Discount rate	0.10%
Dividend yield	0%
Expected term (years)	0.25 - 0.45
Expected volatility	N/A
Probability of milestone achievement	80% - 100%
Strike price	$ 7.80
Fair value of each tranche feature	$0.86 - $3.32

The Series A-1 redeemable convertible preferred tranche liability was settled on March 9, 2021 with the achievement of milestones set forth in the Series A-1 stock purchase agreement. The fair value of the liability was remeasured prior to settlement, resulting in the Company recognizing a loss in the consolidated statement of operations and comprehensive loss of $11.7 million during the year ended December 31, 2021. Immediately thereafter, the balance of the redeemable convertible preferred stock tranche liability of $12.3 million was reclassified to Series A-1 redeemable convertible preferred stock.

A rollforward of the redeemable convertible preferred stock tranche liability is as follows (in thousands):

Balance at December 31, 2020	$	551
Change in fair value		11,718
Settlement upon issuance of Series A-1 redeemable convertible preferred stock		(12,269)
Balance at December 31, 2021	$	—

Note 7. Commitments and Contingencies

Operating Leases

Total rent expense for the years ended December 31, 2021 and 2020 was $248,000 and $51,000, respectively.

In November 2021, the Company entered into an agreement to lease approximately 5,000 square feet of office space in Bellevue, Washington. The term of this lease is for a period of 39 months, which commenced on November 1, 2021. The lease contains rent escalation clauses and an option to extend the term of the lease for an additional 3-year period at a market rate determined according to the lease.

Future minimum lease commitments for non-cancelable operating leases at December 31, 2021, the terms of which expire on various dates through January 31, 2025, are as follows (in thousands)

Year ending December 31,		Amount
2022	$	459
2023		333
2024		172
2025		15
Total minimum lease commitments	$	979

Legal Proceedings

From time to time, the Company may have certain contingent liabilities that arise in the ordinary course of its business activities. The Company accrues a liability for such matters when it is probable that future expenditures will be made and that such expenditures can be reasonably estimated. Significant judgment is required to determine both probability and the estimated amount. As of the date of these consolidated financial statements, we are not party to any material legal matters or claims.

Indemnification

In the ordinary course of business, the Company enters into agreements that may include indemnification provisions. Pursuant to such agreements, the Company may indemnify, hold harmless, and defend an indemnified party for losses suffered or incurred by the indemnified party. Some of the provisions will limit losses to those arising from third-party actions. In some cases, the indemnification will continue after the termination of the agreement. The maximum potential amount of future payments the Company could be required to make under these provisions is not determinable. The Company has never incurred material costs to defend lawsuits or settle claims related to these indemnification provisions. The Company intends to enter into indemnification agreements with its directors and officers that may require the Company to indemnify its directors and officers against liabilities that may arise by reason of their status or service as directors or officers to the fullest extent permitted by Delaware corporate law. The Company currently has directors' and officers' insurance coverage that reduces its exposure and enables the Company to recover a portion of any future amounts paid. The Company believes the estimated fair value of these indemnification agreements in excess of applicable insurance coverage is immaterial.

8. Stock-Based Compensation

2019 Plan

In 2019, the Company adopted the 2019 Equity Incentive Plan (the 2019 Plan). The 2019 Plan provides for the Company to grant qualified stock options, non-qualified stock options, and restricted stock awards to employees, non-employee directors and consultants of the Company under terms and provisions established by the board of directors. Under the terms of the 2019 Plan, options are granted at an exercise price no less than fair value of the Company's common stock on the grant date, except in certain cases related to employees outside of the U.S. However, for any employee who is a 10% or greater stockholder, options are granted at an exercise price no less than 110% of the fair value of the Company's common stock on the grant date. Option awards granted typically have 10-year terms measured from the option grant date. However, if any employee is a 10% or greater stockholder, the awards have 5-year terms measured from the option grant date. While no shares are available for future issuance under the 2019 Plan, it continues to govern outstanding equity awards granted thereunder.

2021 Plan and ESPP

The compensation committee of the Company's board of directors adopted and the Company's stockholders approved the 2021 Equity Incentive Plan (2021 Plan) and the 2021 Employee Stock Purchase Plan (the ESPP), which became effective immediately prior to the effectiveness of the Company's IPO. The 2021 Plan provides for the grant of incentive stock options, non-statutory stock options, restricted stock awards, restricted stock units, stock appreciation rights and other stock-based awards. The Company's employees, officers, directors and consultants are eligible to receive awards under the 2021 Plan. Under the terms of the 2021 Plan, options are granted at an exercise price no less than fair value of the Company's common stock on the grant date, except in certain cases related to significant corporate transactions. Option awards granted typically have 10-year terms measured from the option grant date. As of December 31, 2021, the total number of shares authorized for issuance under the 2021 Plan was 2,558,790. In addition, the number of shares of common stock reserved for issuance under our 2021 Plan will automatically increase on January 1 of each year, beginning on January 1, 2022, and continuing through and including January 1, 2031, by 5% of the total number of shares of common stock outstanding on December 31 of the immediately preceding calendar year, or a lesser number of shares determined by our board prior to the applicable January 1st.

The ESPP allows employees, including executive officers, to contribute up to 15% of their earnings, subject to certain limitations, for the purchase of the Company's common stock at a price per share equal to the lower of (a) 85% of the fair market value of a share of common stock on the first day of the offering period, or (b) 85% of the fair market value of a share of common stock on the last day of the offering period. As of December 31, 2021, there were 255,879 shares of common stock reserved for future issuance under our ESPP plan. The number of shares of common stock reserved for issuance under our ESPP will automatically increase on January 1 of each calendar year, beginning on January 1, 2022 and continuing through and including January 1, 2031, by the lesser of (1) 1% of the total number of shares of our common stock outstanding on December 31 of the preceding calendar year or (2) a number of shares determined by our board. Shares subject to purchase rights granted under our ESPP that terminate without having been exercised in full will not reduce the number of shares available for issuance under the ESPP.

As of December 31, 2021, no shares have been granted or purchased under the ESPP.

Stock Options

Awards with vesting conditions under both plans typically include vesting 25% on the first anniversary of the grant date with the remainder vesting monthly over the following three years.

	Options Outstanding	Weighted Average Exercise Price	Weighted Average Remaining Contract Terms (in years)	Aggregate Intrinsic Values (in thousands)
Balance as of December 31, 2020	435,342	$ 0.52	9.19	$ 415
Options granted	2,591,590	4.07		
Options cancelled and forfeited	(25,551)	1.84		
Options exercised	(79,246)	1.88		457
Balance as of December 31, 2021	2,922,135	$ 3.62	9.14	21,144
Vested and expected to vest, December 31, 2021	2,922,135	$ 3.62	9.14	21,144
Options exercisable as of December 31, 2021	550,292	$ 1.01	8.76	5,219

The aggregate intrinsic value disclosed in the above table is based on the difference between the exercise price of the stock option and the estimated fair value of the Company's common stock as of the respective period-end dates. The weighted-average grant-date fair value of stock options granted during the year ended December 31, 2021 was $7.39 per share.

The Black-Scholes option pricing model for employee and nonemployee stock options incorporates the following assumptions:

Fair Value of Common Stock — Prior to the completion of the Company's IPO, the fair value of the Company's common stock was determined by using straight-line interpolation between the value of common stock derived from valuations performed by independent third party specialists, further described in Note 2 to the consolidated financial statements *Summary of Significant Accounting Policies – Fair Value of Common Stock*. After the completion of the Company's IPO, the fair value of each share of common stock is based on the closing price of the Company's common stock on the date of grant as reported on the Nasdaq Global Market.

Volatility — The expected stock price volatilities are estimated based on the historical and implied volatilities of comparable publicly traded companies as the Company does not have sufficient history of trading its common stock.

Risk-free Interest Rate — The risk-free interest rates are based on US Treasury yields in effect at the grant date for notes with comparable terms as the awards.

Expected Term — The expected term represents the period that the Company's stock options are expected to be outstanding and is determined using the simplified method (based on the mid-point between the vesting date and the end of the contractual term).

Dividend Yield — The expected dividend yield assumption is based on the Company's current expectations about its anticipated dividend policy.

The fair value of the Company's stock option awards was estimated at the date of grant using a Black-Scholes option pricing model with the following assumptions for the years ended December 31, 2021 and 2020:

	Year Ended December 31,	
	2021	2020
Expected term (in years)	5.78 - 6.08	5.70 - 6.12
Expected volatility	77.19% - 79.57%	76.58% - 78.53%
Risk-free interest rate	0.91% - 1.84%	0.36% - 1.47%
Expected dividend yield	0.00%	0.00%

Restricted Stock

The Company has restricted stock awards with service and performance conditions. Awards with a service condition vest 25% on the first anniversary of the grant date and monthly thereafter. Awards with a performance condition will vest upon the Company's initiation of a registrational clinical trial to study the efficacy of ETX-810. The probability of achieving performance conditions is assessed each reporting period. As of December 31, 2021, this performance condition was assessed and deemed not probable, and the Company has recognized no stock-based compensation expense relating to these performance awards. The Company also granted restricted stock awards to employees and non-employees with service conditions that are subject to repurchase by the Company at the original purchase price in the event that the award recipient's employment or relationship is terminated prior to the shares vesting.

The activity for restricted stock awards is as follows:

	Number of Shares	Weighted-Average Grant-Date Fair Value
Unvested at December 31, 2020[(1)]	66,681	$ 1.00
Granted	297,724	$ 8.55
Vested	(32,041)	$ 1.57
Forfeited	—	—
Unvested at December 31, 2021[(2)]	332,364	$ 7.30

(1) Includes 66,750 restricted stock awards granted in 2018 and still outstanding for the period ended December 31, 2020, subject to only performance conditions.

(2) Includes 21,750 restricted stock awards granted in 2018 and still outstanding for the period ended December 31, 2021, subject to only performance conditions.

The fair value of restricted stock awards vested during 2021 was approximately $0.1 million.

The following table sets forth stock-based compensation for stock options, restricted stock awards, and performance awards included in the Company's consolidated statements of operations and comprehensive loss (in thousands):

	Year Ended December 31,	
	2021	2020
Research and development expense	$ 987	$ 334
General and administrative expense	2,750	373
Total stock-based compensation expense	$ 3,737	$ 707

As of December 31, 2021, there was $14.3 million of total unrecognized compensation cost related to unvested stock options and unvested restricted stock awards granted, which is expected to be recognized over a weighted-average period of 3.04 years.

Note 9. Net Loss Per Share Attributable to Common Stockholders

The following table shows the computation of basic and diluted net loss per share (in thousands, except share and per share data):

	Year Ended December 31,	
	2021	2020
Net loss	$ (47,480)	$ (20,668)
Accretion of redeemable convertible preferred stock to redemption value and cumulative preferred stock dividends	(4,548)	(2,285)
Net loss attributable to common stockholders	$ (52,028)	$ (22,953)
Weighted-average shares used in computing net loss per share attributable to common stockholders, basic and diluted	12,260,551	2,187,813
Net loss per share attributable to common stockholders, basic and diluted	$ (4.24)	$ (10.49)

The following outstanding shares of potentially dilutive securities were excluded from the computation of the diluted net loss per share attributable to common stockholders for the periods presented because their effect would have been anti-dilutive:

	Year Ended December 31,	
	2021	2020
Redeemable convertible preferred stock	—	7,140,157
Redeemable convertible preferred stock tranche liability	—	3,717,947
Common stock options	2,922,135	435,342
Unvested restricted stock awards	332,364	66,681
Total potentially dilutive shares	3,254,499	11,360,127

Note 10. Income Taxes

The components of net loss before tax provision from income taxes are as follows (in thousands):

	Year Ended December 31,	
	2021	2020
United States	$ (13,310)	$ (5,076)
United Kingdom	(34,170)	(15,592)
Total	$ (47,480)	$ (20,668)

The following table presents a reconciliation of the Company's expected tax computed at the U.S. statutory federal income tax rate to the total provision for income taxes (in thousands):

	Year Ended December 31,	
	2021	2020
U.S. federal taxes at statutory rate	$ (9,959)	$ (4,340)
State taxes, net of federal benefit	4	1
Foreign rate differential	397	215
Non-deductible expenses	(11)	—
Research credit addback	4,154	1,530
Refundable tax credit	(1,385)	(510)
In-process research and development	—	1,923
Mark-to-market adjustment	2,461	—
Stock-based compensation	480	71
Tax credits	(39)	(72)
U.K. tax rate change impact on deferred income taxes	(1,845)	—
Other, net	219	—
Change in valuation allowance	5,524	1,182
Total	$ —	$ —

The significant components of the Company's deferred tax assets and liabilities are presented below (in thousands):

	Year Ended December 31,	
	2021	2020
Deferred tax assets:		
Stock-based compensation	$ 385	$ 77
Intangible asset	3,834	1,384
Accrued bonus	250	58
Accrued payroll taxes	7	4
Accrued vacation	19	—
Net operating losses	5,866	2,652
Research credits	410	450
Total gross deferred tax assets	10,771	4,625
Deferred tax liabilities:		
Unrealized gain or loss	(89)	(1)
Other	(11)	—
Total gross deferred tax liabilities	(100)	(1)
Valuation Allowance	(10,671)	(4,624)
Net deferred tax liabilities	$ —	$ —

In assessing the realizability of deferred tax assets, the Company considers whether it is more likely than not that some portion or all of the deferred tax assets will not be realized. The ultimate realization of deferred tax assets is dependent upon the generation of future taxable income during the periods in which those temporary differences become deductible. Due to the uncertainty of the business in which the Company operates, projections of future profitability are difficult and past profitability is not necessarily indicative of future profitability. The Company does not believe it is more likely than not that the deferred tax assets will be realized, and accordingly, the Company recorded a valuation allowance of $10.7 million and $4.6 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021, the Company had net operating loss carryforward of approximately $6.0 million for federal income tax purposes, $16.5 million for foreign income tax purposes and $7.3 million for state income tax purposes. These may be used to offset future taxable income. The federal net operation loss carryforward can be carried forward indefinitely while the state net operating loss carryforward will begin to expire in varying amounts in 2039. The Company also has research and development credits of approximately $0.4 million and $0.1 million for federal and state income taxes purposes, respectively. The federal credits may be used to offset future taxable income and will begin to expire in varying amounts in 2039. The state credits may be used to offset future taxable income and will begin to expire in varying amounts in 2040.

The Company is subject to taxation in the U.S. (federal and various states) and the U.K.. Currently, no historical years are under examination. The Company’s tax years starting in December 31, 2018 are open and subject to examination by the U.S. (federal and various states) and the U.K. taxing authorities due to the carryforward of utilized net operating losses and research and development credits.

Uncertain tax positions are recorded when it is more likely than not that a given tax position would not be sustained upon examination by taxing authorities. The Company’s policy for recording interest and penalties related to income taxes, including uncertain tax positions, is to record such items as a component of the provision for income taxes. As of December 31, 2021 and 2020, the Company does not have any uncertain tax positions.

The Company has not completed a Section 382 study to assess whether an ownership change has occurred or whether there have been multiple ownership changes since the Company’s formation. Pursuant to Internal Revenue Code Sections 382 and 383, annual use of the Company’s net operating loss and research and development tax credit carryforwards may be limited in the event a cumulative change in ownership of more than 50% occurs within a three-year period. If eliminated, the related asset would be removed from the deferred tax asset schedule with a corresponding reduction in the valuation allowance. Due to the existence of the valuation allowance, limitations created by future ownership changes, if any, will not impact the Company’s effective tax rate.

Note 11. Asset Acquisition with Related Parties

In October 2020, the Company acquired 100% of the share capital of Athenen Therapeutics, Inc. (the Athenen Acquisition) for a one-for-one exchange of outstanding preferred stock and common stock. As a result, the Company issued a total of 2.5 million Series A preferred shares and 1,550,000 shares of common stock, valued at $5.80 per share and $1.32 per share, respectively, for total purchase consideration of $16.5 million. Additionally, the Company incurred $0.2 million in legal fees related to the acquisition which was included in the value of the IPR&D asset acquired. The IPR&D acquired in this acquisition will enable the Company to develop ETX-155. The Athenen Acquisition is accounted for as an asset acquisition, as substantially all of the fair value of the gross assets acquired is concentrated in a single asset. Since the IPR&D did not have an alternative future use at the time of its acquisition, the Company recognized a charge of $9.2 million during the year ended December 31, 2020 which is included in in-process research and development expense on the consolidated statements of operations and comprehensive loss. RA Capital Healthcare Fund L.P. was a greater than 10% owner of the Company and Athenen prior to the acquisition.

Assets acquired and liabilities assumed in Athenen Acquisition (in thousands)		
In-process research and development	$	9,158
Cash		8,279
Other assets and liabilities, net		(694)
Total net assets acquired	$	16,743

Note 12. Related Party Transactions

Services Provided by Related Parties

The Company has a services agreement with Carnot, LLC. Carnot, LLC was subsequently dissolved and the services agreement transitioned to its successor Carnot Pharma, LLC. The Company reimburses Carnot Pharma, LLC for research and development expenses incurred on its behalf. RA Capital Management, L.P. is the manager of the members of Carnot, LLC and Andrew Levin, a member of our board of directors and former CEO, is the President of Carnot Pharma, LLC. Adam Rosenberg, a member of our board of directors, is a Venture Partner at Carnot Pharma, LLC dba RA Ventures. Amounts invoiced and reimbursed for the years ended December 31, 2021 and 2020 were approximately $1.3 million and $0.6 million, respectively. See Note 11 for details on assets acquired from related parties.

Note 13. Defined Contribution Plan

The Company began sponsoring a 401(k) defined contribution plan in 2020. Participation in the plan is available to substantially all US-based employees. Company contributions to the plan are discretionary. The Company made matching contributions of up to 4% of each participating employee's eligible compensation. Total expense recognized from the 401(k) matching contributions for the years ended December 31, 2021 and 2020 was approximately $0.1 million and $20,000, respectively.

The Company also has a workplace pension contribution scheme for U.K.-based employees. For the years ended December 31, 2021 and 2020, the Company made discretionary contributions of approximately $0.1 million and $42,000 in excess of the minimum statutory requirements, respectively.

Note 14. Subsequent Events

For purposes of the consolidated financial statements as of December 31, 2021 and the year then ended, the Company evaluated subsequent events for recognition and measurement purposes through March 7, 2022, the date the consolidated financial statements were issued.

Grants of Stock Options under 2021 Plan

In the first quarter of 2022, the Company granted additional options for the purchase of an aggregate of 1,295,412 shares of common stock, at an exercise price of $8.21 per share, to employees including executive management. The aggregate grant date-fair value of these awards was $7.2 million, which is expected to be recognized as stock-based compensation expense over a weighted-average period of 4.0 years.

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

None.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

Disclosure controls and procedures (as defined in Rule 13a-15(e) and 15d-15(e) under the Exchange Act) are designed to ensure that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our Chief Executive Officer and principal financial officer or persons performing similar functions, as appropriate to allow timely decisions regarding required disclosure.

Based on our evaluation, the Chief Executive Officer and Chief Financial Officer, have concluded that the Company's disclosure controls and procedures (as such term is defined in Rule(s) 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended) were not effective as of December 31, 2021 because of the material weaknesses in our internal control over financial reporting described below.

Material Weaknesses in Internal Control Over Financial Reporting

Management identified material weaknesses in our internal control over financial reporting. A material weakness is a deficiency, or combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of the annual or interim consolidated financial statements will not be prevented or detected on a timely basis. The material weaknesses are as follows:

- We did not design or maintain an effective control environment. Specifically, we lacked a sufficient number of professionals with an appropriate level of accounting knowledge, training and experience to appropriately analyze, record and disclose accounting matters commensurate with accounting and reporting requirements. The lack of personnel contributed to additional material weaknesses.
- We did not design and maintain formal accounting policies, procedures and controls to achieve complete, accurate and timely financial accounting, reporting and disclosures, including segregation of duties and controls over the preparation and review of journal entries, account reconciliations and consolidation.

These material weaknesses did not result in a misstatement to the consolidated financial statements. However, these material weaknesses could result in a misstatement of our account balances or disclosures that would result in a material misstatement of our annual or interim consolidated financial statements that would not be prevented or detected.

- We did not design and maintain effective controls over information technology (IT) general controls for information systems that are relevant to the preparation of our consolidated financial statements. Specifically, we did not design and maintain (a) program change management controls to ensure that information technology program and data changes affecting financial IT applications and underlying accounting records are identified, tested, authorized and implemented appropriately, (b) user access controls to ensure appropriate segregation of duties and that adequately restrict user and privileged access to financial applications, programs, and data to appropriate Company personnel, (c) computer operations controls to ensure that critical batch jobs are monitored, and data backups are authorized and monitored, and (d) testing and approval controls for program development to ensure that new software development is aligned with business and IT requirements.

These IT deficiencies did not result in a misstatement to the consolidated financial statements. However, the IT deficiencies, when aggregated, could impact maintaining effective segregation of duties, as well as the effectiveness of IT-dependent controls (such as automated controls that address the risk of material misstatement to one or more assertions, along with the IT controls and underlying data that support the effectiveness of system-generated data and reports) that could result in misstatements potentially impacting all financial statement accounts and disclosures that would not be prevented or detected. Accordingly, management has determined the IT deficiencies in the aggregate constitute a material weakness.

Management has concluded that these material weaknesses in internal control over financial reporting were due to the fact that we were recently a private company with limited resources and did not have the necessary business processes and related internal controls formally designed and implemented, coupled with the appropriate resources with the appropriate level of experience and technical expertise, to oversee our business processes and controls.

Notwithstanding the above identified material weaknesses, management believes the consolidated financial statements as included in Item 8 of this Annual Report on Form 10-K present fairly, in all material respects, the Company's financial condition, results of operations and cash flows as of and for the periods presented in accordance with generally accepted accounting principles in the United States.

Remediation Efforts to Address Material Weaknesses

We have implemented, and are continuing to implement, measures designed to improve internal control over financial reporting to remediate the control deficiencies that led to our material weaknesses by, among other things, hiring qualified personnel with appropriate expertise to perform specific functions and ensure adequate segregation of key duties and responsibilities, and designing and implementing improved policies, processes and internal controls, including ongoing senior management review and audit committee oversight. Further, we are implementing new financial systems to improve segregation of duties and controls and reliability of system generated data.

The actions that have been taken are subject to continued review, implementation and testing by management, as well as oversight by the audit committee of our board of directors. While we have implemented a variety of steps to remediate these weaknesses, we cannot assure you that we will be able to fully remediate them, which could impair our ability to accurately and timely meet our public company reporting requirements.

Management's Report on Internal Control Over Financial Reporting

This report does not include a report of management's assessment regarding internal control over financial reporting or an attestation report of our registered public accounting firm due to a transition period established by rules of the SEC for newly public companies.

Changes in Internal Control over Financial Reporting

Other than in connection with the implementation of the remedial measures described above, there have not been any changes in our internal control over financial reporting (as such term is defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during the quarter ended December 31, 2021 that have materially affected, or are reasonably likely to materially affect our internal control over financial reporting.

Item 9B. Other Information.

Not applicable.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

Information required by this item and not set forth below will be set forth in the sections headed *Election of Directors* and *Executive Officers* contained in our definitive Proxy Statement to be filed with the Commission within 120 days after the conclusion of our year ended December 31, 2021 (the "Proxy Statement") pursuant to General Instructions G(3) of Form 10-K and is incorporated herein by reference.

We have adopted a code of business conduct and ethics that applies to our directors, officers and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. A current copy of our code of business conduct and ethics is available under the Corporate Governance section of our website at www.eliemtx.com. If we make any substantive amendments to the code of business conduct and ethics or grants any waiver from a provision of the code of business conduct and ethics to any executive officer or director that are required to be disclosed pursuant to SEC rules, we will promptly disclose the nature of the amendment or waiver on our website or in a current report on Form 8-K.

Item 11. Executive Compensation.

The information required by this item will be set forth in our Proxy Statement in the sections headed *Executive and Director Compensation* and *Director Compensation* contained in our Proxy Statement and is incorporated herein by reference.

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

Information required by this item will be set forth in the sections headed *Security Ownership of Certain Beneficial Owners and Management* and *Executive and Director Compensation* contained in our Proxy Statement and is incorporated herein by reference.

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

Information required by this item will be set forth in the sections headed *Certain Related-Person Transactions* and *Information Regarding the Board of Directors and Corporate Governance* contained in our Proxy Statement and is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services.

Information required by this item will be set forth in the sections headed *Ratification of Selection of Independent Registered Public Accounting Firm* contained in our Proxy Statement and is incorporated herein by reference.

PART IV

Item 15. Exhibits, Financial Statement Schedules.

(a) Documents filed as part of this report

(1)Financial Statements. The following consolidated financial statements of Eliem Therapeutics, Inc., together with the report of PricewaterhouseCoopers LLP, an independent registered public accounting firm, required to be filed pursuant to Part II, Item 8 of this Annual Report on Form 10-K are included on the following pages:

(2)Financial Statement Schedules. None.

(3)List of exhibits required by Item 601 of Regulation S-K. See part (b) below.

(b)Exhibits.

Exhibit Index

Exhibit Number	Description of Exhibit	Incorporated by Reference			
		Form	File No.	Exhibit	Filing Date
2.1	Unit Transfer Agreement, dated February 4, 2019, by and between the Registrant and the Members of NeoKera, LLC.	S-1	333-257980	2.1	July 16, 2021
2.2	Asset Contribution Agreement, dated February 4, 2019, by and between the Registrant and Carnot, LLC.	S-1	333-257980	2.2	July 16, 2021
2.3	Agreement and Plan of Merger and Reorganization, dated October 15, 2020, by and among the Registrant, Athena Merger Sub Inc., Athenen Therapeutics, Inc., AI ETI LLC, as Eliem Representative and Adam Rosenberg, as Athenen Representative.	S-1	333-257980	2.3	July 16, 2021
3.1	Amended and Restated Certificate of Incorporation of the Registrant.	8-K	001-40708	3.1	August 12, 2021
3.2	Amended and Restated Bylaws of the Registrant.	S-1	333-257980	3.4	August 2, 2021
4.1	Form of common stock certificate of the Registrant.	S-1	333-257980	4.1	August 2, 2021
4.3*	Description of Securities				
10.1	Amended and Restated Investor Rights Agreement, dated May 21, 2021, by and among the Registrant and the investors listed on Schedule A thereto.	S-1	333-257980	10.1	July 16, 2021
10.2+	2021 Equity Incentive Plan.	S-1	333-257980	10.4	August 2, 2021
10.3+	Forms of Option Agreement, Stock Option Grant Notice and Notice of Exercise under the 2021 Equity Incentive Plan.	S-1	333-257980	10.5	August 2, 2021
10.4+	Forms of Restricted Stock Unit Grant Notice and Restricted Stock Unit Award Agreement under the 2021 Equity Incentive Plan.	S-1	333-257980	10.6	August 2, 2021
10.5+	2021 Employee Stock Purchase Plan.	S-1	333-257980	10.7	August 2, 2021
10.6	Form of Indemnification Agreement, by and between the Registrant and each of its directors and executive officers.	S-1	333-257980	10.8	August 2, 2021
10.7+	Executive Employment Agreement by and between the Registrant and Robert Azelby, effective October 1, 2021, as amended.	S-1	333-257980	10.9	August 2, 2021
10.8+	Executive Employment Agreement by and between the Registrant and Erin M. Lavelle, effective October 1, 2021, as amended.	S-1	333-257980	10.10	August 2, 2021
10.9+	Executive Employment Agreement by and between Eliem Therapeutics (UK) Ltd. and Valerie Morisset, Ph.D., effective January 1, 2021.	S-1	333-257980	10.11	July 16, 2021

21.1	List of subsidiaries.	S-1	333-257980	21.1	August 2, 2021
23.1*	Consent of Independent Registered Public Accounting Firm.				
31.1*	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.				
31.2*	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.				
32.1*	Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.				
32.2*	Certification of Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.				
101.INS*	XBRL Instance Document				
101.SCH*	XBRL Taxonomy Extension Schema Document				
101.CAL*	XBRL Taxonomy Extension Calculation Linkbase Document				
101.DEF*	XBRL Extension Definition Linkbase Document				
101.LAB*	XBRL Taxonomy Label Linkbase Document				
101.PRE*	XBRL Taxonomy Extension Presentation Linkbase Document				
104*	Cover Page Interactive Data File (embedded within inline XBRL document)				

* Filed herewith.
+ Indicates management contract or compensatory Plan.

Item 16. Form 10-K Summary

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, as amended, the Registrant has duly caused this Report to be signed on its behalf by the undersigned, thereunto duly authorized**.**

Eliem Therapeutics, Inc.

Date: March 7, 2022

By: /s/ Robert Azelby
Robert Azelby
President and Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this Report has been signed below by the following persons on behalf of the Registrant in the capacities and on the dates indicated.

Name	Title	Date
/s/ Robert Azelby **Robert Azelby**	President, Chief Executive Officer and Director *(Principal Executive Officer)*	March 7, 2022
/s/ Erin M. Lavelle **Erin M. Lavelle**	Executive Vice President, Chief Operating Officer and Chief Financial Officer *(Principal Financial and Accounting Officer)*	March 7, 2022
/s/ Andrew Levin **Andrew Levin, M.D., Ph.D.**	Chairman of the Board of Directors	March 7, 2022
/s/ Judith Dunn **Judith Dunn, Ph.D.**	Director	March 7, 2022
/s/ Leone Patterson **Leone Patterson**	Director	March 7, 2022
/s/ Liam Ratcliffe **Liam Ratcliffe, M.D., Ph.D.**	Director	March 7, 2022
/s/ Adam Rosenberg **Adam Rosenberg**	Director	March 7, 2022
/s/ Simon Tate **Simon Tate**	Director	March 7, 2022

Exhibit 4.3

DESCRIPTION OF THE REGISTRANT'S SECURITIES

REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES

EXCHANGE ACT OF 1934

The following is a description of the common stock, $0.0001 par value per share ("Common Stock") of Eliem Therapeutics, Inc. (the "Company," "we," "our," or "us"), which is the only security of the Company registered pursuant to Section 12 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). The following summary description is based on the provisions of our Amended and Restated Certificate of Incorporation (the "Certificate of Incorporation"), our Amended and Restated Bylaws, (the "Bylaws"), and the applicable provisions of the Delaware General Corporation Law (the "DGCL"). This information may not be complete in all respects and is qualified entirely by reference to the provisions of our Certificate of Incorporation and our Bylaws. Our Certificate of Incorporation and our Bylaws are filed as exhibits to our Annual Report on Form 10-K of which this exhibit is a part. We also provide a summary of our preferred stock, which is not registered under Section 12 of the Exchange Act.

Authorized Capital Shares

Our authorized capital stock consists of 250,000,000 shares of common stock, $0.0001 par value per share, and 10,000,000 shares of preferred stock, par value $0.0001 per share. In addition, under our Certificate of Incorporation, our board of directors may, without further action by our stockholders, fix the rights, preferences, privileges and restrictions of up to an aggregate of 10,000,000 shares of preferred stock in one or more series and authorize their issuance. These rights, preferences and privileges could include dividend rights, conversion rights, voting rights, terms of redemption, liquidation preferences and the number of shares constituting any series or the designation of such series, any or all of which may be greater than the rights of common stock. Any issuance of preferred stock could adversely affect the voting power of holders of common stock and the likelihood that such holders would receive dividend payments and payments on liquidation. In addition, the issuance of preferred stock could have the effect of delaying, deterring or preventing a change of control or other corporate action. As of December 31, 2021, we have no shares of preferred stock issued and outstanding. We have no present plans to issue any shares of preferred stock. For a complete description of the terms and provisions of the Company's preferred stock refer to our Certificate of Incorporation and Bylaws.

Common Stock

Voting Rights

Each holder of common stock is entitled to one vote for each share on all matters submitted to a vote of the stockholders, including the election of directors. Under our Certificate of Incorporation, our stockholders do not have cumulative voting rights. Because of this, the holders of a majority of the shares of common stock entitled to vote in any election of directors can elect all of the directors standing for election. These provisions in our Certificate of Incorporation could discourage potential takeover attempts. See "Certificate of Incorporation and Bylaws" below.

Dividend Rights

Subject to preferences that may apply to any then-outstanding preferred stock, the holders of common stock are entitled to receive ratably those dividends, if any, as may be declared from time to time by the board of directors out of legally available funds. We do not anticipate paying any cash dividends in the foreseeable future.

Liquidation Rights

In the event of our liquidation, dissolution or winding up, holders of common stock will be entitled to share ratably in the net assets legally available for distribution to stockholders after the payment of all of our debts and other liabilities and the satisfaction of any liquidation preference granted to the holders of any then-outstanding shares of preferred stock.

Preemptive or Similar Rights

Holders of common stock have no preemptive, conversion or subscription rights and there are no redemption or sinking fund provisions applicable to the common stock. The rights, preferences and privileges of the holders of

common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of preferred stock that we may designate in the future.

Anti-Takeover Provisions

Section 203 of the Delaware General Corporation Law

We are subject to Section 203 of the DGCL, which generally prohibits a publicly held Delaware corporation from engaging in any business combination with any interested stockholder for a period of three years after the date that such stockholder became an interested stockholder, with the following exceptions:

- before such date, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;
- upon completion of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction began, excluding for purposes of determining the voting stock outstanding, but not the outstanding voting stock owned by the interested stockholder, those shares owned (1) by persons who are directors and also officers and (2) employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or
- on or after such date, the business combination is approved by the board of directors and authorized at an annual or special meeting of the stockholders, and not by written consent, by the affirmative vote of at least 66 2/3% of the outstanding voting stock that is not owned by the interested stockholder.

In general, Section 203 defines a “business combination” to include the following:

- any merger or consolidation involving the corporation and the interested stockholder;
- any sale, transfer, pledge or other disposition of 10% or more of the assets of the corporation involving the interested stockholder;
- subject to certain exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;
- any transaction involving the corporation that has the effect of increasing the proportionate share of the stock or any class or series of the corporation beneficially owned by the interested stockholder; or
- the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits by or through the corporation.

In general, Section 203 defines an “interested stockholder” as an entity or person who, together with the person’s affiliates and associates, beneficially owns or within three years prior to the time of determination of interested stockholder status did own, 15% or more of the outstanding voting stock of the corporation.

A Delaware corporation may “opt out” of these provisions with an express provision in its original certificate of incorporation or an express provision in its Certificate of Incorporation or Bylaws resulting from a stockholders’ amendment approved by at least a majority of the outstanding voting shares. We have not opted out of these provisions. As a result, mergers or other takeover or change in control attempts of us may be discouraged or prevented.

Certificate of Incorporation and Bylaws

Among other things, our Certificate of Incorporation and Bylaws:

- permit our board of directors to issue up to 10,000,000 shares of preferred stock, with any rights, preferences and privileges as they may designate, including the right to approve an acquisition or other change of control;
- provide that the authorized number of directors may be changed only by resolution of our board of directors;
- provide that our board of directors is classified into three classes of directors;

- provide that, subject to the rights of any series of preferred stock to elect directors, directors may only be removed for cause, which removal may be effected, subject to any limitation imposed by law, by the holders of at least 66 2/3% of the voting power of all of our then-outstanding shares of the capital stock entitled to vote generally at an election of directors;
- provide that all vacancies, including newly created directorships, may, except as otherwise required by law, be filled by the affirmative vote of a majority of directors then in office, even if less than a quorum;
- require that any action to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders and not be taken by written consent or electronic transmission;
- provide that stockholders seeking to present proposals before a meeting of stockholders or to nominate candidates for election as directors at a meeting of stockholders must provide advance notice in writing, and also specify requirements as to the form and content of a stockholder's notice;
- provide that special meetings of our stockholders may be called only by the chairperson of our board of directors, our chief executive officer or by our board of directors pursuant to a resolution adopted by a majority of the total number of authorized directors; and
- not provide for cumulative voting rights, therefore allowing the holders of a majority of the shares of common stock entitled to vote in any election of directors to elect all of the directors standing for election, if they should so choose.

The amendment of any of these provisions requires approval by the holders of at least 66 2/3% of the voting power of all of our then-outstanding capital stock entitled to vote generally in the election of directors, voting together as a single class.

The combination of these provisions makes it more difficult for our existing stockholders to replace our board of directors as well as for another party to obtain control of us by replacing our board of directors. Since our board of directors has the power to retain and discharge our officers, these provisions could also make it more difficult for existing stockholders or another party to effect a change in management. In addition, the authorization of undesignated preferred stock makes it possible for our board of directors to issue preferred stock with voting or other rights or preferences that could impede the success of any attempt to change our control.

These provisions are intended to enhance the likelihood of continued stability in the composition of our board of directors and its policies and to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to reduce our vulnerability to hostile takeovers and to discourage certain tactics that may be used in proxy fights. However, such provisions could have the effect of discouraging others from making tender offers for our shares and may have the effect of delaying changes in our control or management. As a consequence, these provisions may also inhibit fluctuations in the market price of our stock.

Choice of Forum

Our Certificate of Incorporation provides that the Court of Chancery of the State of Delaware will be the exclusive forum for actions or proceedings brought under Delaware statutory or common law: (1) any derivative action or proceeding brought on our behalf; (2) any action asserting a breach of fiduciary duty; (3) any action asserting a claim against us arising under the DGCL; (4) any action regarding our Certificate of Incorporation or Bylaws; (5) any action as to which the DGCL confers jurisdiction to the Court of Chancery of the State of Delaware; or (6) any action asserting a claim against us that is governed by the internal affairs doctrine. Our Certificate of Incorporation further provides that the federal district courts of the United States of America will be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act of 1933, as amended. Such provision is intended to benefit and may be enforced by us, our officers and directors, employees and agents. Although Certificate of Incorporation contains the choice of forum provisions described above, it is possible that a court could find one or more of these provisions inapplicable for a particular claim or action or that such provision is unenforceable. Further, notwithstanding anything in our Certificate of Incorporation and Bylaws, investors cannot waive compliance with the federal securities laws and regulations thereunder. The choice of forum provisions will not apply to suits brought to enforce any liability or duty created by Exchange Act or any other claim for which the federal courts have exclusive jurisdiction.

If any action the subject matter of which is within the scope described above is filed in a court other than a court located within the State of Delaware (a "Foreign Action"), in the name of any stockholder, such stockholder shall be

deemed to have consented to the personal jurisdiction of the state and federal courts located within the State of Delaware in connection with any action brought in any such court to enforce the applicable provisions of our Certificate of Incorporation and Bylaws and having service of process made upon such stockholder in any such action by service upon such stockholder's counsel in the Foreign Action as agent for such stockholder.

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 any of our directors, officers, other employees or stockholders, which may discourage lawsuits with respect to such claims or make such lawsuits more costly for stockholders, although our stockholders will not be deemed to have waived our compliance with federal securities laws and the rules and regulations thereunder.

Exchange Listing

Our common stock is listed on the Nasdaq Global Market under the symbol "ELYM."

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company, LLC. The transfer agent's address is 6201 15th Avenue, Brooklyn, New York 11219 and the telephone number is (800) 937-5449.

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statement on Form S-8 (No. 333-258771) of Eliem Therapeutics, Inc. of our report dated March 7, 2022 relating to the financial statements, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP
Seattle, Washington
March 7, 2022

Exhibit 31.1

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Robert Azelby, certify that:

(1) I have reviewed this Annual Report on Form 10-K for the fiscal year ended December 31, 2021 of Eliem 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)) 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) 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

(c) 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: March 7, 2022

By: /s/ Robert Azelby
Robert Azelby
President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Erin M. Lavelle, certify that:

(1) I have reviewed this Annual Report on Form 10-K for the fiscal year ended December 31, 2021 of Eliem 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)) 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) 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

(c) 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: March 7, 2022

By: /s/ Erin M. Lavelle
Erin M. Lavelle
Chief Operating Officer and Chief Financial Officer
(Principal Financial and Accounting Officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of Eliem Therapeutics, Inc. (the "Company") for the period ending December 31, 2021, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that:

(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 result of operations of the Company.

Date: March 7, 2022

By: /s/ Robert Azelby
Robert Azelby
President and Chief Executive Officer
(Principal Executive Officer)

The foregoing certification is being furnished solely to accompany the Report pursuant to 18 U.S.C. § 1350, and is not being filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, and is not to be incorporated by reference into any filing of the Company, whether made before or after the date hereof, regardless of any general incorporation language in such filing. A signed original of this written statement required by Section 906 has been provided to the Company and will be retained by the Company and furnished to the Securities and Exchange Commission or its staff upon request.

Exhibit 32.2

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of Eliem Therapeutics, Inc. (the "Company") for the period ending December 31, 2021, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that:

(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 result of operations of the Company.

Date: March 7, 2022

By: /s/ Erin M. Lavelle
Erin M. Lavelle
Chief Operating Officer and Chief Financial Officer
(Principal Financial and Accounting Officer)

The foregoing certification is being furnished solely to accompany the Report pursuant to 18 U.S.C. § 1350, and is not being filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, and is not to be incorporated by reference into any filing of the Company, whether made before or after the date hereof, regardless of any general incorporation language in such filing. A signed original of this written statement required by Section 906 has been provided to the Company and will be retained by the Company and furnished to the Securities and Exchange Commission or its staff upon request.