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: 001-37378

ATYR PHARMA, INC.

(Exact name of registrant as specified in its charter)

Delaware	**20-3435077**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
3545 John Hopkins Court, Suite #250, San Diego, CA	**92121**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code (858) 731-8389

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

Title of each class	Trading Symbol	Name of each exchange on which registered
Common Stock, par value $0.001 per share	**LIFE**	**The Nasdaq Capital 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, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

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

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

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

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

The aggregate market value of the registrant's voting and non-voting common equity held by non-affiliates of the registrant was approximately $76,202,853 based on the closing price of the registrant's common stock on the Nasdaq Capital Market of $4.88 per share on June 30, 2021, the last business day of the registrant's most recently completed second fiscal quarter. Shares of common stock held by each executive officer and director have been excluded from this calculation. This determination of affiliate status may not be conclusive for other purposes.

The number of outstanding shares of the registrant's common stock, par value $0.001 per share, as of March 10, 2022 was 27,795,794.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement to be filed with the Securities and Exchange Commission (SEC), pursuant to Regulation 14A in connection with the registrant's 2022 Annual Meeting of Stockholders, which will be filed subsequent to the date hereof, are incorporated by reference into Part III of this Annual Report on Form 10-K. Such proxy statement will be filed with the SEC not later than 120 days following the end of the registrant's fiscal year ended December 31, 2021.

ATYR PHARMA, INC.

ANNUAL REPORT ON FORM 10-K

For the Fiscal Year Ended December 31, 2021

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In this Annual Report on Form 10-K (Annual Report), unless the context requires otherwise, "aTyr Pharma," "aTyr," "Company," "we," "our," and "us" means aTyr Pharma, Inc. and our subsidiary, Pangu BioPharma Limited.

The market data and certain other statistical information used in this Annual Report are based on independent industry publications, governmental publications, reports by market research firms or other independent sources. Some data are also based on our good faith estimates. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information.

We own various U.S. federal trademark applications and unregistered trademarks, including our company name. All other trademarks or trade names referred to in this Annual Report are the property of their respective owners. Solely for convenience, the trademarks and trade names in this Annual Report are referred to without the symbols ® and ™, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto.

Forward-Looking Statements

In addition to historical information, this Annual Report and the information incorporated herein by reference contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (Securities Act) and Section 21E of the Securities Exchange Act of 1934, as amended (Exchange Act) including statements regarding our business, our financial position, the research and development of biopharmaceutical products, the timing of clinical trial activities and other statements describing our goals, expectations, intentions or beliefs. These statements include but are not limited to statements under the captions "Business" and "Management's Discussion and Analysis of Financial Condition and Results of Operations", as well as other sections in this Annual Report. Such statements reflect our current views and assumptions and are subject to risks and uncertainties, particularly those inherent in the process of developing and commercializing biopharmaceutical products. Actual results could differ materially from those discussed in this Annual Report. Factors that could cause or contribute to such differences include, but are not limited to, those identified in Part I, Item 1A "Risk Factors" beginning on page 24 of this Annual Report, as well as those discussed in our other filings with the Securities and Exchange Commission (SEC). As a result, you are cautioned not to unduly rely on these forward-looking statements. We disclaim any duty to update any forward-looking statement to reflect events or circumstances that occur after the date on which such statement is made.

Risk Factors Summary

Below is a summary of the principal factors that make an investment in our securities speculative or risky. This summary does not address all of the risks that we face. Additional discussion of the risks summarized in this risk factors summary, and other risks that we face, can be found in Part I, Item 1A "Risk Factors" and should be carefully considered, together with other information in this Annual Report and our other filings with the SEC before making investment decisions regarding our securities.

Investing in our securities involves substantial risk. The risks described under Part I, Item 1A "Risk Factors" beginning on page 24 of this Annual Report may cause us to not realize the full benefits of our strengths or may cause us to be unable to successfully execute all or part of our strategy. Some of the more significant risks we face include the following:

- We will need to raise additional capital or enter into strategic partnering relationships to fund our operations;
- We are a pre-commercial biotherapeutics company and have incurred significant losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future;
- We may encounter substantial delays and other challenges in our planned clinical trials or we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities;
- If we are unable to successfully complete or otherwise advance clinical development, obtain regulatory or marketing approval for, or successfully commercialize our therapeutic product candidates, including efzofitimod (the non-proprietary name for ATYR1923) and ATYR2810, or experience significant delays in doing so, our business will be materially harmed;
- Our current product candidates and any other product candidates that we may develop from our discovery engine represent novel therapeutic approaches, which may cause significant delays or may not result in any commercially viable drugs;
- Our therapeutic product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following marketing approval, if any;
- We depend on our existing collaborations and may depend on collaborations with additional third parties for the development and commercialization of certain of our product candidates. If our collaborations are not successful, we may not be able to capitalize on the market potential of these product candidates;
- If we are unable to obtain, maintain or protect intellectual property rights related to our product candidates, or if the scope of such intellectual property protection is not sufficiently broad, we may not be able to compete effectively in our markets;
- Our business could continue to be adversely affected by the effects of the ongoing COVID-19 pandemic; and
- Our future success depends on our ability to retain key employees, consultants and advisors and to attract, retain and motivate qualified personnel.

PART I

Item 1. Business.

We are a biotherapeutics company engaged in the discovery and development of innovative medicines based on novel biological pathways. We have concentrated our research and development efforts on a newly discovered area of biology, the extracellular functionality and signaling pathways of tRNA synthetases. Built on more than a decade of foundational science on extracellular tRNA synthetase biology and its effect on immune responses, we have built a global intellectual property estate directed to a potential pipeline of protein compositions derived from 20 tRNA synthetase genes and their extracellular targets, such as neuropilin-2 (NRP2).

Our lead therapeutic candidate, efzofitimod (the non-proprietary name for ATYR1923), is a fusion protein comprised of the immunomodulatory domain of histidyl-tRNA synthetase fused to the fragment crystallizable (Fc) region of a human antibody, and serves as a selective modulator of NRP2 that downregulates innate and adaptive immune response in inflammatory disease states. We are developing efzofitimod as a potential disease-modifying therapy for patients with fibrotic lung diseases with high unmet medical need. This includes interstitial lung diseases (ILD), a group of rare immune-mediated disorders that cause progressive fibrosis of the lung. In December 2018, we designed a Phase 1b/2a multiple-ascending dose, double-blind, placebo-controlled clinical trial in patients with pulmonary sarcoidosis, a major form of ILD, to evaluate the safety, tolerability, immunogenicity and steroid-sparing effect of efzofitimod, and conduct other exploratory assessments of efficacy, such as lung function. In September 2021, we announced positive results and clinical proof-of-concept from the Phase 1b/2a clinical trial in 37 patients with pulmonary sarcoidosis. Efzofitimod was safe and well-tolerated at all doses administered with no serious drug-related adverse events or signal of immunogenicity. Additionally, the study demonstrated consistent dose response for efzofitimod on key efficacy endpoints and improvements compared to placebo, including measures of steroid reduction, lung function, pulmonary sarcoidosis symptom measures and inflammatory biomarkers. Based on the results of this study, we met with the U.S. Food and Drug Administration (FDA) in February 2022 and presented these data and our plans for subsequent clinical development and path to registration for efzofitimod for the treatment of pulmonary sarcoidosis. As a result of the meeting, we intend to initiate a planned registrational trial of efzofitimod in the third quarter of 2022. Based on the results of the Phase 1b/2a clinical trial, we believe efzofitimod has potential applications in the treatment of other ILDs, such as chronic hypersensitivity pneumonitis (CHP) and connective tissue disease related ILD (CTD-ILD).

In January 2020, we entered into a collaboration and license agreement (Kyorin Agreement) with Kyorin Pharmaceutical Co., Ltd. (Kyorin) for the development and commercialization of efzofitimod for the treatment of ILD in Japan. Under the Kyorin Agreement, Kyorin received an exclusive right to develop and commercialize efzofitimod in Japan for all forms of ILD, and is obligated to fund all research, development, regulatory, marketing and commercialization activities in Japan. In September 2020, Kyorin began dosing patients in a Phase 1 clinical trial of efzofitimod (known as KRP-R120 in Japan) and completed the last subject visit in December 2020. The Phase 1 clinical trial, which was conducted and funded by Kyorin, was a placebo-controlled clinical trial to evaluate the safety, pharmacokinetics (PK) and immunogenicity of efzofitimod in 32 healthy Japanese male volunteers. Efzofitimod was observed to be generally well-tolerated with no drug-related serious adverse events, and PK findings were consistent with previous studies of efzofitimod. We received an $8.0 million upfront payment in January 2020 and a $2.0 million milestone payment in January 2021 upon completion of enrollment in the Phase 1 clinical trial, and we are eligible to receive up to an additional $165.0 million in the aggregate upon achievement of certain development, regulatory and sales milestones, as well as tiered royalties ranging from the mid-single digits to mid-teens on net sales in Japan.

In January 2022, the FDA granted efzofitimod an orphan drug designation for the treatment of sarcoidosis.

In parallel with our clinical development of efzofitimod, we have been advancing our discovery pipeline of NRP2 antibodies and tRNA synthetases. In November 2020, we announced ATYR2810 as our lead Investigational New Drug (IND) candidate in oncology from our NRP2 antibody program. ATYR2810 is a fully humanized monoclonal antibody that is designed to specifically and functionally block the interaction between NRP2 and one of its primary ligands, vascular endothelial growth factor (VEGF). NRP2 is a pleiotropic cell surface receptor that is highly expressed on certain tumors and increased NRP2 expression is associated with worse outcomes in many cancers, such as overall survival, metastasis and resistance to targeted therapies. The role of NRP2 and VEGF signaling in the tumor microenvironment and its importance in the progression of certain aggressive cancers is becoming increasingly validated. ATYR2810 is in preclinical development for the potential treatment of certain aggressive cancers where NRP2 is implicated, and we plan to initiate a Phase 1 clinical trial in the second half of 2022.

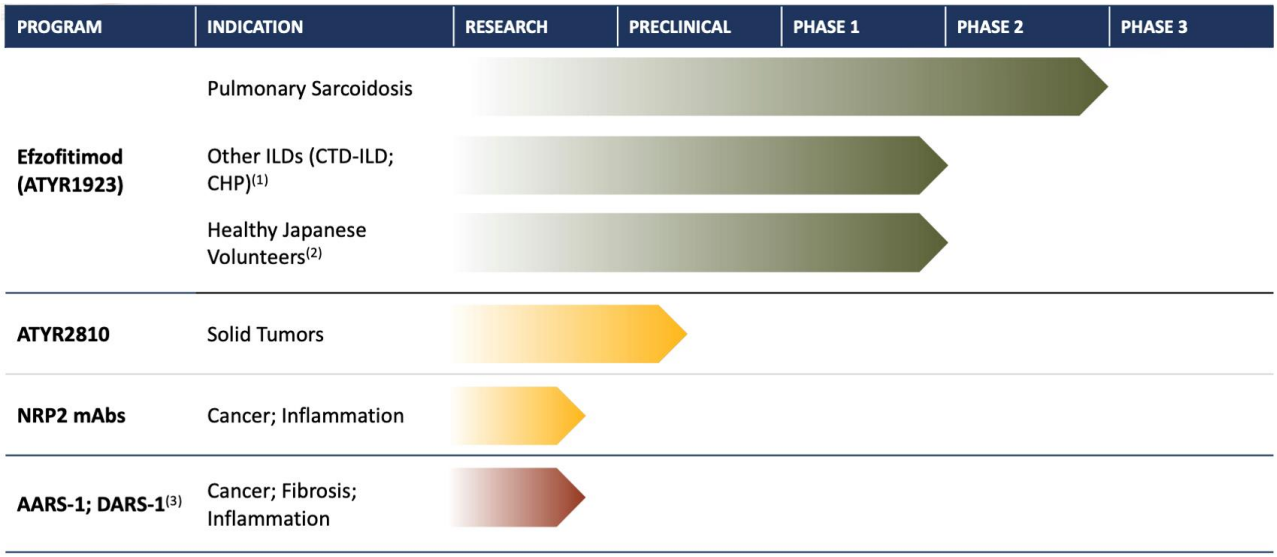
In March 2020, our subsidiary, Pangu BioPharma Limited (Pangu BioPharma), together with the Hong Kong University of Science and Technology (HKUST) was awarded a grant of approximately $750,000 to build a high-throughput platform for the development of bi-specific antibodies. The project is being funded by the Hong Kong government's Innovation and Technology Commission (ITC) under the Partnership Research Program (PRP). The PRP aims to support research and development projects undertaken by companies in collaboration with local universities and public research institutions. The ITC funded approximately 50% of the total estimated project cost, and we contributed the remaining 50%. The term of the project was initially for two years and in

December 2021, due to complications arising from the ongoing COVID-19 pandemic, was extended for an additional six months with no additional costs. In May 2021, we announced that Pangu and HKUST achieved certain milestones for the first year of the project.

In February 2021, we announced two new discovery programs from our tRNA synthetase platform. These programs will investigate the functionality of selected fragments of Alanyl-tRNA synthetase (AARS) and Aspartyl-tRNA synthetase (DARS) in immunology, fibrosis and cancer. We are also advancing our preclinical pipeline of tRNA synthetases and NRP2 targeting candidates through internal research efforts, industry and academic collaborations.

The impacts of the ongoing COVID-19 pandemic on our business have included the delay in enrollment of our now completed Phase 1b/2a clinical trial in patients with pulmonary sarcoidosis and the discontinuation of some patients in that trial, temporary closures of portions of our facilities and those of our licensees and collaborators, disruptions or restrictions on our employees' ability to travel and delays in certain research and development activities. Other potential impacts to our business include, but are not limited to disruptions to or delays in other clinical trials, third-party manufacturing supply and other operations, the potential diversion of healthcare resources away from the conduct of clinical trials to focus on pandemic concerns, interruptions or delays in the operations of the FDA or other regulatory authorities, and our ability to raise capital and conduct business development activities.

Therapeutic Candidate Pipeline



(1) CTD-ILD: connective tissue disease-related ILD (e.g. Scleroderma-related ILD); CHP: chronic hypersensitivity pneumonitis
(2) In partnership with Kyorin Pharmaceutical Co., Ltd. Kyorin's Phase 1 study in healthy Japanese volunteers has been completed. Kyorin is eligible to participate in future efzofitimod trials sponsored by aTyr.
(3) The next two candidates from our tRNA synthetase platform; initial focus on NK cell biology

Strategy

Key elements of our strategy include the following:

Develop efzofitimod to address unmet medical needs within fibrotic lung diseases. Based on the positive results and clinical proof-of-concept from our efzofitimod Phase 1b/2a clinical trial in September 2021, we believe we can expedite development of efzofitimod for pulmonary sarcoidosis toward regulatory approval. In addition, the positive results from our efzofitimod Phase 1b/2a trial, as well as funding from the Kyorin Agreement, could give us the opportunity to potentially launch additional Phase 2 clinical trials of efzofitimod for both CHP and CTD-ILD.

Develop ATYR2810 to address unmet medical needs within certain aggressive cancers where NRP2 is implicated and continue to expand our knowledge on the therapeutic potential of NRP2 antibodies by utilizing our leadership position in this emerging area of biology. NRP2 is a receptor that plays a key role in lymphatic development and in regulating inflammatory responses. In many forms of cancer, high NRP2 expression is associated with worse outcomes. These associations may represent new therapeutic drug opportunities, such as ATYR2810. We are currently focused on completing IND enabling studies to enable us to commence clinical development of ATYR2810. We are committed to translating this area of newly discovered biology to therapeutic applications, both through our internal research and academic collaborations.

Build a diverse pipeline of biologics product candidates based on our understanding of extracellular tRNA synthetase biology. We believe the positive results and clinical proof-of-concept from our efzofitimod Phase 1b/2a clinical trial in September 2021 validate our tRNA synthetase biology platform. We continue to deepen our expertise in the production of biologic product candidates based on tRNA synthetases with the goal of developing programs with multiple therapeutic modalities. We believe we have proven this with the announcement of our AARS and DARS discovery programs. Through our internal research efforts and both industry and academic collaborators, we intend to further our product development efforts in this area.

Efzofitimod

Overview of Efzofitimod

We are developing efzofitimod as a potential therapeutic for patients with fibrotic lung diseases. Our primary focus is in ILD, a group of rare immune-mediated fibrotic lung disorders with significant unmet medical need. Efzofitimod works by selectively modulating NRP2 to downregulate the innate and adaptive immune responses in uncontrolled inflammatory disease states to resolve inflammation and prevent subsequent fibrosis. Pre-clinically, we have demonstrated the therapeutic potential of efzofitimod in a number of preclinical models of lung injury, fibrosis and inflammation, both *in vitro* and in rodents. We have also characterized the pathways by which efzofitimod exerts its immunomodulatory effects. In June 2018, we announced data from a first-in-human Phase 1 clinical trial of efzofitimod conducted in Australia. This randomized, double-blind, placebo-controlled study investigated the safety, tolerability, immunogenicity, and PK of intravenous efzofitimod in 36 healthy volunteers. In the study, the drug was observed to be generally well-tolerated at all dose levels tested, with no significant adverse events and the observed PK profile supported the potential for a once-monthly dosing regimen.

A comprehensive review of the preclinical and Phase 1 data in consultation with key opinion leaders led to our selection of pulmonary sarcoidosis as the first clinical indication for efzofitimod, as well as our belief of the potential of efzofitimod to treat other fibrotic lung diseases.

In September 2021, we announced positive results and clinical proof-of-concept from a Phase 1b/2a clinical trial in 37 patients with pulmonary sarcoidosis. Efzofitimod was safe and well-tolerated at all doses with no drug-related serious adverse events or signal of immunogenicity. Additionally, the study demonstrated consistent dose response for efzofitimod on key efficacy endpoints and improvements compared to placebo, including measures of steroid reduction, lung function, sarcoidosis symptom measures and inflammatory biomarkers. Based on the results of this study, we met with the FDA in February 2022 and presented these data and our plans for subsequent clinical development and path to registration for efzofitimod for pulmonary sarcoidosis. We intend to initiate a planned registrational trial in the third quarter of 2022. Based on the results of the Phase 1b/2a clinical trial, we believe efzofitimod has potential applications in the treatment of other ILD, such as CHP and CTD-ILD.

Background and Mechanism of Action

Efzofitimod is a novel immunomodulatory Fc fusion protein in development for the treatment of fibrotic lung diseases. Efzofitimod is a selective modulator of NRP2 that downregulates innate and adaptive immune responses at a cellular level in uncontrolled inflammatory disease states and prevents subsequent fibrosis.

Efzofitimod is a novel molecular entity comprised of a human 59 amino acid protein fused to the Fc region of human immunoglobulin 1 (IgG1). It acts as an extracellular immunomodulator. The amino acid sequence of the active moiety corresponds identically to the extracellularly active immunomodulatory domain of histidyl-tRNA synthetase (HARS) amino acids 2 to 60 (HARS 2-60).

The gene for HARS gives rise to a number of splice variants, and though most of these have lost their catalytic activity, they all retain the N-terminal domain (HARS amino acids 2-60). This N-terminal domain, non-essential for the enzyme’s protein synthesis activity that is required in all living organisms, was appended to HARS during the evolutionary development of multicellular organisms and retained with high sequence identity across mammalian species, but is not found in lower organisms. One splice variant (SV9), which encodes only the N-terminal domain of the protein, is enriched in human lung tissue. Expression of this HARS splice variant is increased following inflammatory cytokine stimulation (IFN-g and TNF-a, two key players in the initiation of lung inflammation and fibrosis) followed by subsequent secretion, indicating it is being regulated in response to local inflammation. Furthermore, HARS, specifically the N-terminal domain, is targeted by autoantibodies in a rare autoimmune disorder (known as anti-Jo-1 syndrome). Anti-Jo-1 syndrome is characterized by extensive activation and migration of immune cells into lung and muscle and is classically associated with the triad of ILD, myositis, and arthritis. It is hypothesized that the sequestration of HARS may play a causal role through disruption of its homeostatic immune-regulatory effects.

NRP2 was identified as the sole binding partner for efzofitimod through screening via a cell microarray system in which over 4,500 cell surface proteins are represented. This screening approach identified two NRP2 isoforms (Neuropilin 2A and 2B) as the only convincing and specific binding partners of efzofitimod. The binding site was confirmed to be within the “turn” of the helix-turn-helix

structure of the HARS N-terminal domain comprised within efzofitimod. Binding of efzofitimod is specific to NRP2 with no observable cross-reactivity to NRP1, which is the most closely related cell surface receptor in both protein sequence and structure. A domain that is structurally similar (but divergent in protein sequence) to the HARS N-terminal domain (termed the WHEP domain) is found in other amino-acyl tRNA synthetases, yet these domains do not exhibit binding to NRP2, indicating this is a highly specific interaction. Interestingly, binding of efzofitimod occurs in a manner distinct from the more well-characterized ligands of NRP2 including VEGF and semaphorin 3F (SEMA3F), and does not interfere with NRP2 dimerization with their co-receptors. Thus, the HARS N-terminus appears to be a newly discovered ligand for NRP2, as opposed to an antagonist. The discovery of the HARS N-terminus/NRP2 signaling axis represents a previously unknown mechanism of biological regulation, in which this novel ligand of NRP2 may act as a homeostatic regulator of aberrant immune responses.

NRP2 is a cell surface receptor that is present on multiple immune cell types, including certain myeloid cells and subsets of T-cells. NRP2 expression is often upregulated upon inflammatory insult or stimulation. Growing evidence indicates that NRP2 predominantly influences myeloid cell biology such as activation and recruitment to inflammatory sites. For instance, NRP2 expression on alveolar macrophages regulates airway inflammatory responses to inhaled lipopolysaccharide. In sarcoidosis, NRP2 expression has been shown to be localized within the sarcoid granulomas, highly expressed in Langhans giant cells which are myeloid in nature.

Efzofitimod has been shown to significantly reduce lung inflammation and fibrosis, reduce immune cell trafficking to the lung and improve respiratory function parameters in multiple animal models of lung fibrosis. Furthermore, efzofitimod has demonstrated consistent downregulatory effects on inflammatory and pro-fibrotic cytokines and chemokines in both animal disease models and human clinical trials. Efzofitimod appears to primarily impact IL-6, TNF-a, IFN-g, MCP-1 and IP-10, markers that have been implicated in the pathology of fibrotic lung diseases.

Efzofitimod is a potential first-in-class immunomodulator that may present a novel mechanism of action to therapeutically control or balance immune responses that are drivers of lung fibrosis.

Preclinical Development

Our preclinical estate of translational animal models was selected to help inform and de-risk clinical development of efzofitimod. We have evaluated the biological activity and safety of efzofitimod across a diverse set of experimental fibrotic lung disease models, representative of the four major forms of ILD (sarcoidosis, CHP, CTD-ILD and idiopathic pulmonary fibrosis (IPF)), as well as in normal animals, looking for signals of activity and potential biomarkers, while confirming tolerability and a favorable safety profile.

In these models, efzofitimod has significantly reduced histological lung fibrosis and inflammation, restored normal lung function, reduced lung protein levels of several inflammation and fibrosis-related cytokines and chemokines (e.g. IFN-γ, MCP-1/CCL2, IL-6) and reduced counts of immune cells in bronchoalveolar lavage (BAL) central to ILD pathology (e.g., neutrophils). These data have been presented in posters at key respiratory conferences over the past several years (e.g. the American Thoracic Society (ATS) International Congress) and are available for review on our website.

Efzofitimod and NRP2 receptor

NRP2 is known to be expressed on a number of different immune cell types that play a key role in regulating inflammatory responses. Efzofitimod is a fusion protein combining a novel immunomodulatory domain from HARS and a human IgG1 Fc. Efzofitimod inhibits cytokines and chemokines involved in the regulation of inflammatory and fibrotic responses and reduces inflammation-and fibrosis in animal models of ILD. Efzofitimod has previously demonstrated potent immunomodulatory activity *in vitro* and *in vivo*. We sought to characterize the molecular basis for efzofitimod's immunomodulatory properties and demonstrated that efzofitimod specifically and selectively binds to NRP2 on the cell surface. These findings indicate that modulation of the NRP2 signaling pathway with efzofitimod could be a novel therapeutic approach to immune-mediated and fibrotic diseases such as pulmonary sarcoidosis.

Sarcoidosis is characterized by the formulation of granulomas, clumps of inflammatory cells found in one or more organs of the body and denoted by the presence of Langhans giant cells which are myeloid in nature. NRP2 was shown to be expressed in samples obtained from lung and skin of sarcoidosis patients with high NRP2 expression detected on key immune cells known to play an important role in inflammation and granuloma formation, including the Langhans giant cells. In work carried out in collaboration with Dr. Elliot Crouser's laboratory at The Ohio State University utilizing an established *ex vivo* assay of granuloma formation, it was demonstrated that an efzofitimod analog containing the identical immunomodulatory HARS domain exhibited statistically significant reduction of granuloma formation generated from sarcoid peripheral blood mononuclear cells (PBMCs). Given the importance of granulomas in the pathology and progression of pulmonary sarcoidosis and the known ability of efzofitimod to disrupt inflammatory

responses, we hypothesize that efzofitimod may play a role in regulating sarcoid granuloma formation. These findings highlight the potential of efzofitimod to exert its effect on various immune cells directly related to the pathology of the target patient population.

These data were presented in posters at the ATS International Virtual Meeting in August 2020 and the European Society International Congress in September 2021.

Based on our translational biology program, which demonstrated activity across distinct experimental animal models either driven by direct lung injury or systemic pathology, along with our understanding of efzofitimod's mechanism of action, we decided to move the program forward into patient clinical trials in ILD.

ILD, Pulmonary Sarcoidosis, and the Role of Immunology

The current primary target population for efzofitimod is ILD, a group of immune-mediated disorders which can cause progressive fibrosis of the lung. There are over 200 different types of ILD, of which the four major forms are: pulmonary sarcoidosis, CHP, CTD-ILD, and IPF. We have focused our development efforts on progressive, immune-mediated forms of ILD, with limited therapeutic options, that has the potential to be impacted by efzofitimod. These lung conditions are recognized as having a measurable immune-mediated pathology, involving both innate and adaptive immune mechanisms that contribute to pathogenesis, and can result in progressive disease leading to fibrosis and death. The first ILD that we are investigating clinically is pulmonary sarcoidosis.

Sarcoidosis is an inflammatory disease of unknown cause, characterized by the formation of granulomas, clumps of inflammatory cells in one or more organs in the body. Sarcoidosis affects people of all ages, with the incidence peaking at 20 to 39 years of age. The disorder usually begins in the lungs, skin or lymph nodes, but can affect almost any organ. Sarcoidosis in the lungs is called pulmonary sarcoidosis and affects over 90% of sarcoidosis patients. Estimates of prevalence vary, but generally indicate that approximately 200,000 Americans are currently living with pulmonary sarcoidosis. The prognosis for patients with pulmonary sarcoidosis ranges from benign and self-limiting to chronic, debilitating fibrotic disease and mortality.

The immunopathogenesis of sarcoidosis is not yet well understood. A leading hypothesis is that granuloma formation involves the interplay between antigen, human leukocyte antigen class II molecules, and T-cell receptors: a presumptive sarcoid antigen is engulfed by circulating antigen-presenting cells (APCs; macrophages, dendritic cells) and the subsequent interplay between APCs and CD4+ T-cells initiates granuloma formation. T-lymphocyte activation subsequently plays a crucial role in sarcoidosis pathogenesis.

For patients with pulmonary sarcoidosis, the primary goal of treatment is to improve the patient's symptoms and quality of life, while secondarily managing the inflammation associated with the granulomas that could lead to the development of more permanent fibrosis and impairment of pulmonary function. Efzofitimod may provide a therapeutic benefit in pulmonary sarcoidosis by providing an immunomodulatory function to help resolve inflammation. Moreover, the mechanism of action of efzofitimod in T-cells and macrophages potentially overlaps with the cellular pathology observed in pulmonary sarcoidosis. In preclinical studies, efzofitimod has been observed to inhibit cytokines involved in regulation of inflammatory and immune responses and attenuate T-cell activation, while also modulating macrophage endosome maturation. Related to our mechanistic studies, we have also discovered that NRP2 is up-regulated during activation of myeloid cells including macrophages, dendritic cells and neutrophils, and that efzofitimod can bind to NRP2 on these cell types. Furthermore, efzofitimod has been observed to significantly reduce inflammation-dependent pulmonary fibrosis and improve respiratory function parameters in bleomycin-induced animal models of ILD, particularly when administered during the inflammatory phase of the disease. We believe that by inhibiting the chronic inflammatory response in these patients, efzofitimod may be able to restore immune balance and prevent progressive fibrosis, thereby providing a safer, potentially more effective alternative to oral corticosteroids (OCS) and other immunosuppressive therapies that currently comprise the standard of care for patients with symptomatic pulmonary sarcoidosis.

Clinical Development

Efzofitimod Phase 1b/2a Clinical Trial –Pulmonary Sarcoidosis

We initiated a proof-of-concept Phase 1b/2a clinical trial for efzofitimod in December 2018. The Phase 1b/2a clinical trial was a randomized, double-blind, placebo-controlled multiple-ascending dose, first-in-patient study with IV efzofitimod in 37 patients. The study was conducted in patients with pulmonary sarcoidosis undergoing an OCS tapering regimen, in three cohorts of 12 patients each, at dose levels of 1.0 mg/kg, 3.0 mg/kg and 5.0 mg/kg.

The primary objective of the study was to evaluate safety and tolerability of multiple ascending doses of efzofitimod. Secondary objectives included assessment of the potential steroid-sparing effects of efzofitimod. In addition, efzofitimod's PK and immunogenicity following multiple dose administration were evaluated. Additional endpoints of interest included the exploratory assessment of the efficacy of efzofitimod for the treatment of pulmonary sarcoidosis by evaluating changes over time in: fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT lung imaging; lung function assessed by percent predicted forced vital capacity (FVC% predicted) and diffusing capacity of the lungs for carbon monoxide; serum biomarkers of

interest; health-related quality of life assessments and questionnaires; and measurement of skin lesions (for patients with cutaneous involvement at baseline).

This study consisted of three staggered dose cohorts. Each cohort consisted of three periods: a screening period, a 20-week placebo-controlled treatment period, and a four-week follow-up period ending with final study assessments at Week 24. Within each cohort, 12 patients were randomized 2:1 to efzofitimod (N=8) or placebo (N=4). Study drug was administered via IV infusion every four weeks for a total of six doses (20 weeks of treatment). The efzofitimod doses levels being evaluated were 1.0 mg/kg, 3.0 mg/kg and 5.0 mg/kg. Starting on Day 15 patients began a taper (reduction) in OCS according to specific guidelines from their starting dose of 10-25 mg/day of prednisone (or equivalent) to a target dose of 5.0 mg/day, to be completed on or before Day 50. The OCS dose was tapered through Week 24 and patients were followed for the remainder of the study to determine their ability to maintain on this 5.0 mg dose. Optionally, further reductions in the OCS dose to below 5.0 mg/day may be attempted after the Week 16 visit, if determined by the investigator to be feasible. Patients who required an increase in OCS dose at any time in the study were to continue to receive blinded study drug and be followed through to the end of the study.

In September 2021, we announced positive results and clinical proof-of-concept from the Phase 1b/2a clinical trial in 37 patients with pulmonary sarcoidosis. Efzofitimod was safe and well-tolerated at all doses with no drug-related serious adverse events or signal of immunogenicity. Additionally, the study demonstrated consistent dose response for efzofitimod on key efficacy endpoints and improvements compared to placebo, including measures of steroid reduction, lung function, sarcoidosis symptom measures and inflammatory biomarkers. Key safety and clinical efficacy findings for efzofitimod from the study include:

- Safe and well-tolerated at all doses:
    - No dose-relationship with most common adverse events associated with underlying disease;
    - No drug-related serious adverse events; and
    - No signal of immunogenicity.
- Dose response and consistent positive findings across key efficacy endpoints:
    - Steroid reduction of 58% overall from baseline and 22% relative reduction compared to placebo in steroid usage post taper in the 5.0 mg/kg treatment group;
    - Complete steroid taper to 0 mg achieved and maintained for 33% of patients in the 5.0 mg/kg treatment group compared to no patients in any other group;
    - Absolute improvement in forced vital capacity (FVC) as a measure of lung function at week 24 of 3.3% in the 5.0 mg/kg treatment group compared to placebo, with an improvement in FVC of > 2.5%, considered clinically meaningful;
    - Clinically meaningful improvement over placebo observed for dyspnea (shortness of breath), cough, fatigue and the King’s Sarcoidosis Scores for Lung and General Health in 5.0 mg/kg treatment group;
    - Dose dependent trends of improvement in key inflammatory biomarkers compared to placebo including IL-6, MCP-1, IFN-γ, IP-10 and TNFa as well as key sarcoidosis markers including ACE, IL-2Ra and SAA with tightest control in the 5.0 mg/kg treatment group; and
    - FDG-PET-CT was not evaluable due to incomplete data primarily caused by operational issues related to the ongoing COVID-19 pandemic.

Efzofitimod Phase 2 Clinical Trial – COVID-19 with Severe Respiratory Complications

In response to the ongoing COVID-19 pandemic, we conducted a Phase 2 clinical trial of efzofitimod in patients with COVID-19 related severe respiratory complications. The study was designed to evaluate the safety ad preliminary efficacy of efzofitimod compared to placebo through the assessment of key clinical outcome measures. In early 2021, we reported positive data which showed that the trial met its primary endpoint of safety, demonstrating that a single, intravenous (IV) dose of efzofitimod was observed to be generally safe and well-tolerated in both the 1.0 and 3.0 mg/kg treatment groups, with no drug-related serious adverse events. The study also showed a signal of activity in the 3.0 mg/kg cohort. In addition, patients treated with efzofitimod demonstrated a trend of overall improvement in key biomarkers analyzed compared to placebo. We plan on leveraging data from our efzofitimod Phase 2 clinical trial in COVID-19 patients with severe respiratory complications for our mechanistic understanding of efzofitimod and for its application in ILD.

Efzofitimod Phase 1 Clinical Trial – Healthy Volunteers

In June 2018, we announced results of our first-in-human Phase 1 clinical trial of efzofitimod conducted in Australia. This randomized, double-blind, placebo-controlled study evaluated the safety, tolerability, immunogenicity, and PK of IV efzofitimod in healthy volunteers. The Phase 1 clinical trial enrolled 36 healthy volunteers who were randomized to one of six sequential cohorts and received a single infusion of IV efzofitimod or placebo. Ascending efzofitimod doses by cohort ranged from 0.03 mg/kg to 5.0 mg/kg. The results indicate that the drug was observed to be generally well-tolerated at all dose levels tested, with no significant adverse events or induction of anti-drug antibodies observed following efzofitimod dosing or throughout the one-month follow-up period. The PK profile of efzofitimod following single-dose administration was linear across the evaluated dose range. Higher efzofitimod doses yielded sustained serum concentrations through the end of the one-month follow-up period that were above the predicted therapeutic threshold, supporting the potential for a once-monthly dosing regimen.

Kyorin Agreement

In January 2020, we entered into the Kyorin Agreement for the development and commercialization of efzofitimod for ILD in Japan. Under the terms of the Kyorin Agreement, Kyorin received exclusive rights to develop and commercialize efzofitimod in Japan for all forms of ILD and is obligated to fund all research, development, regulatory, marketing and commercialization activities in Japan. We are responsible for supplying all drug product for Japan, as well as supporting development activities for efzofitimod. In September 2020, Kyorin began dosing of its Phase 1 clinical trial of efzofitimod (known as KRP-R120 in Japan) and completed the last subject visit in December 2020. The Phase 1 trial, which was conducted and funded by Kyorin, was a placebo-controlled study to evaluate the safety, PK and immunogenicity of efzofitimod in 32 healthy Japanese male volunteers. Efzofitimod was observed to be generally well-tolerated with no drug-related serious adverse events, and PK findings were consistent with previous studies of efzofitimod. We received an $8.0 million upfront payment in January 2020 and a $2.0 milestone payment in January 2021 upon completion of enrollment in the Phase 1 clinical trial, and we are eligible to receive up to an additional $165.0 million in the aggregate upon achievement of certain development, regulatory and sales milestones, as well as tiered royalties ranging from the mid-single digits to mid-teens on net sales in Japan.

Unless earlier terminated, the term of the Kyorin Agreement continues until the expiration of the royalty obligations. Either party may terminate the Kyorin Agreement in the event that the other party breaches the agreement and fails to cure the breach, becomes insolvent or challenges certain of the intellectual property rights licensed under the agreement.

ATYR2810

Overview of ATYR2810

We have generated a panel of antibodies to selectively target distinct domains of NRP2, including those interacting with VEGF, semaphorins and certain chemokines/chemokine receptors, such as CCL21/CCR7. NRP2 interacts with several different protein ligands individually through these distinct domains to mediate signaling through diverse biological pathways associated with different disease states, creating an opportunity to modulate different aspects of NRP2-mediated signaling selectivity for distinct therapeutic applications.

ATYR2810 is the first IND candidate to arise from our internal research program designing monoclonal antibodies to selectively target the NRP2 receptor and its associated signaling pathways. ATYR2810 is a fully humanized monoclonal antibody that specifically and functionally blocks the interaction between NRP2 and one of its primary ligands VEGF. ATYR2810 is currently in preclinical development for the potential treatment of certain aggressive cancers where NRP2 is implicated, and we plan to initiate a Phase 1 clinical trial in the second half of 2022.

NRP2 is highly expressed in certain highly aggressive, solid tumors, the lymphatic system and on key immune cells implicated in cancer progression, including tumor associated macrophages and myeloid derived suppressor cells, among others. Increased NRP2 expression is associated with negative outcomes in many cancers, including resistance to targeted therapies, metastasis and worsened overall survival. VEGF is a validated mediator of tumor growth and plays a role in immune evasion in the tumor microenvironment. The role of NRP2 and VEGF signaling in the tumor microenvironment and its importance in the progression of certain aggressive cancers, such as breast cancer, renal cell carcinoma and lung cancer, is becoming increasingly validated. Blocking VEGF signaling through NRP2 is a differentiated approach from targeting VEGF or VEGF-R, directly in that current therapeutic approaches do not disrupt this pathway. Antibodies that can selectively block different aspects of the NRP2 signaling pathway, including the NRP2/VEGF axis, may have therapeutic potential in aggressive cancers where NRP2 is implicated.

Preclinical Development

We believe we have generated a body of compelling preclinical data in both human-derived and animal models that suggest that ATYR2810 could be effective against certain types of solid tumors, including highly aggressive tumors such as triple-negative breast cancer and non-small cell lung cancer. There is a growing body of evidence that expression of NRP2 is enriched in treatment-resistant,

dedifferentiated cancer cells expressing mesenchymal markers. Furthermore, NRP2/VEGF signaling is implicated in enhanced tumor metastasis promoted by the process of epithelial-to-mesenchymal transition (EMT) in breast cancer. ATYR2810 blocks binding of VEGF to NRP2 and has demonstrated tumor inhibitory effects and increased sensitivity to chemotherapy in solid tumor models.

In triple-negative breast cancer patient-derived organoids (PDO), as well as patient-derived tumor xenograft (PDX) models, ATYR2810 administered in combination with widely used anti-cancer therapeutics, including the chemotherapeutic agent cisplatin or the targeted VEGF antibody bevacizumab—increased the anti-tumor effects of each agent. Furthermore, treatment with ATYR2810 was shown to downregulate genes associated with EMT and stemness, in particular down-regulating expression of Zeb1, a central regulator of these processes. EMT is the acquisition of mesenchymal or stem cell-like features by epithelial cells in the tumor that confer migratory and invasive properties to these cells. EMT is of great importance in the tumor microenvironment regulating tumor growth, progression, and metastatic cascade, as well as being implicated in tumor evasion of the immune system. The data suggests that ATYR2810's ability to impact EMT may be one mechanism by which it mediates its anti-tumor effects and demonstrates the therapeutic potential of inhibiting EMT through blocking the NRP2/VEGF signaling axis in various types of solid tumors.

In addition to triple-negative breast cancer, we have also generated data suggesting efficacy in other solid tumor models, including non-small cell lung cancer, both as a single agent and in combination with chemotherapy.

ATYR2810's ability to promote the differentiation of aggressive tumor cells away from a stem cell phenotype and render them more susceptible to conventional cancer therapies has the potential to be a significant advancement because therapy resistance, which is associated with tumor recurrence and metastasis, is a major challenge for patients with aggressive cancers. These findings suggest that targeting the NRP2/VEGF pathway may be an effective therapeutic strategy for breast cancer and potentially other aggressive solid tumors where many patients remain unresponsive to currently available treatments.

ATYR2810 is currently undergoing IND-enabling studies.

Our Discovery Engines

NRP2 Biology

We are actively working on NRP2 receptor biology pathways of interest to select additional product candidates for preclinical and clinical investigation in a variety of disease settings through efforts internally, as well as through collaborations with academic institutions.

NRP2 is a pleiotropic cell surface receptor that was originally identified based on its role in axon guidance during neuronal development, and subsequently shown to be important in the development of the lymphatic and immune system. Importantly, NRP2 can bind to multiple ligands and co-receptors to influence these multiple functional roles, including interaction with type 3 semaphorins and plexins to impact neural development, and also forms of vascular endothelial growth factor, especially VEGF-C which is involved in lymphogenesis.

Recent evidence suggests that there are high levels of NRP2 expression found on multiple immune cell types, which may play important roles in migration, antigen presentation, phagocytosis and cell-to-cell interactions. NRP2 is expressed in various cells of the immune system such as B-cells, T-cells, natural killer (NK) cells, neutrophils, dendritic cells and macrophages, including alveolar macrophages. It plays an important role in the regulation of immune cell activation and migration including endosome maturation, the modulation of autophagy and efferocytosis. This suggests that NRP2 may be an important regulator of biological responses in a number of different disease settings with potential for therapeutic intervention.

We are collaborating with leading academic groups working on these pathways and we are excited to contribute to advancing the understanding of NRP2 biology and how it may play a role in treating certain diseases. We continue to research the ways in which NRP2 utilizes common mechanisms, including VEGFs and semaphorins, to regulate diverse pathways. We believe our growing evidence base of data on the functions of NRP2 will allow us to select and develop additional novel product candidates for various diseases with unmet medical need.

tRNA Synthetase Biology

Extracellular tRNA synthetase biology represents a novel set of potential physiological modulators and therapeutic targets.

Using efzofitimod as a model, we have developed a process to advance novel tRNA synthetase domains from a concept to therapeutic candidate. This process leverages our early discovery work as well as current scientific understanding of tRNA synthetase evolution, protein structure, gene splicing and tissue-specific regulation to identify potentially active protein domains. Screening approaches are employed to identify target cells and extracellular receptors for these tRNA synthetase-derived proteins. These cellular systems can then be used in mechanism-of-action studies to elucidate the role these proteins play in cellular responses and their

potential therapeutic utility. We are working to identify new tRNA synthetase based drug candidates through our internal discovery efforts and academic collaborations.

AARS/DARS

Utilizing our novel approach, we identified target cells and potential receptors for fragments of AARS and DARS, gaining insights into their potential biological activity in immunology, cancer and fibrosis. This includes data demonstrating that these extracellular tRNA synthetase fragments bind to innate and adaptive immune cells, including macrophages and NK cells. NK cells have emerged as an important therapeutic target in cancer immunotherapy. In 2022, we plan to further elucidate the therapeutic potential of these additional tRNA synthetase molecules through mechanistic investigations, including *in vitro* and *in vivo* preclinical studies.

Hong Kong University of Science and Technology

In October 2007, we formed our Hong Kong subsidiary, Pangu BioPharma to support our basic and translational research in tRNA synthetase biology. We hold 98% of the outstanding shares of Pangu BioPharma, and a subsidiary of HKUST holds the remaining outstanding shares. Pangu BioPharma originally collaborated with HKUST on the discovery and development of aminoacyl tRNA synthetase protein therapeutics. Beginning in July 2008, Pangu BioPharma, in collaboration with HKUST, entered into a series of three research grant agreements with the Government of the Hong Kong Special Administrative Region to carry out research in the discovery and development of tRNA synthetase biology. Following the completion of the research grants, Pangu BioPharma funded research with respect to development of aminoacyl tRNA synthetase protein therapeutics pursuant to annual joint research agreements. As a result of work performed under these agreements, HKUST researchers with support from Pangu BioPharma were instrumental in discovering a splice variant of HARS that liberates the smaller, active HARS amino acid 2-60 from the full-length tRNA synthetase and has been shown to modulate the immune system. To date, HKUST researchers have discovered over 200 novel compositions that are covered in issued patents and have published six articles detailing their research in peer-reviewed scientific journals.

In March 2020, we announced that Pangu BioPharma, together with HKUST, was awarded a grant of approximately $750,000 to build a high-throughput platform for the development of bi-specific antibodies. Initially this research will focus on diseases, including cancer, in which NRP2 overexpression is strongly implicated. A bi-specific antibody approach presents a further differentiated opportunity to elucidate the therapeutic potential of NRP2 and its co-receptors as drug targets. The fact that NRP2 interacts directly with various co-receptor molecules, including certain plexins, integrins and chemokine receptors like CCR7, makes it a prime target for bi-specific antibodies that can target both receptors simultaneously and modulate the activity of these signaling complexes. The project is being funded by the Hong Kong Government’s Innovation and Technology Commission (ITC) under the Partnership Research Program. The ITC funded approximately 50% of the total estimated project cost, and we contributed the remaining 50%. In April 2020, we entered a research grant agreement with HKUST and the Hong Kong Special Administrative Region for this grant (the Grant Agreement). The term of the project was initially for two years and in December 2021, due to the ongoing COVID-19 pandemic, was extended for an additional six months with no additional cost.

In May 2021, we announced that Pangu and HKUST achieved the milestones set forth for the first year of the project. Key milestones achieved for the first year of the project included building out a highly-skilled research team to establish an innovative antibody discovery platform at HKUST. An integral part of this project was the development and implementation of a novel single-cell antibody discovery approach which yielded numerous candidate high-affinity NRP2/co-receptor antibodies targeting VEGFR3 and PlexinA1 being screened in functional assays. The second year of the project aims to identify the most productive pairings, optimize mid-scale production/purification and prioritize lead candidate bi-specific antibodies based on activity in therapeutically relevant cell-based assays. Bi-specific antibody approaches are increasingly being considered as a novel and differentiated approach to relevant targets and present a unique pipeline opportunity for us to explore.

Pangu BioPharma is the sole beneficial owner of all resulting intellectual property rights from the research performed under these agreements, subject to the right of HKUST’s subsidiary to use certain background intellectual property of HKUST in conducting the research and, in the event Pangu BioPharma applies for individual funding of any work under the research programs, compliance with the terms and conditions of any written agreement covering ownership of such funded works. In addition, the Grant Agreement requires the completion of the research project for the assignment of intellectual property rights.

We are also party to a license agreement with Pangu BioPharma, pursuant to which Pangu BioPharma has granted us an exclusive, royalty-bearing license (with a right to sublicense) in and to certain of Pangu BioPharma’s solely and jointly owned patent rights and know-how to research, develop, manufacture, use, import, export, distribute, offer for sale, sell and have sold products incorporating such patent rights and know-how for any therapeutic, prognostic or diagnostic use throughout the world.

Competition

The biotechnology and pharmaceutical industries are intensely competitive. We will face competition with respect to our current product candidates and any other therapeutics we may develop or commercialize in the future, from pharmaceutical companies, biotechnology companies, universities and other research institutions. Our competitors may have substantially greater financial, technical and other resources, such as larger research and development staff and established marketing, sales and manufacturing organizations. Additional mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or licensing on an exclusive basis, drug products that are more effective, safer or less costly than any product candidate that we may develop.

Although we believe we are the only company engaged in the discovery and development of therapeutics based on novel functions of tRNA synthetases and NRP2 receptor biology, we are aware of other companies that could compete with our product candidates as described below.

Efzofitimod

For patients with pulmonary sarcoidosis, the primary goal of treatment is typically to improve the patient's quality of life, while secondarily managing the inflammation that could lead to the development of more permanent fibrosis and impairment of pulmonary function. Currently, the only FDA-approved therapies for the treatment of sarcoidosis are prednisone, a generic corticosteroid, and H.P. Acthar Gel, a repository corticotropin injection marketed globally by Mallinckrodt plc, which was approved in 1952 and is not widely used by physicians due to toxicity and cost issues. The consensus standard of care for pulmonary sarcoidosis is immune-modulatory therapy. First line treatment is typically with OCS that act mainly by suppressing inflammatory genes. OCS therapy has been shown to stabilize or improve disease symptoms in some patients, although relapse commonly occurs once OCS therapy is tapered or discontinued. Long-term OCS use is associated with significant side effects including substantial weight gain, development of insulin resistance, osteoporosis, and risk of infection. Alternatives, such as cytotoxic immunosuppressive agents (e.g., methotrexate) have been used as steroid-sparing agents, however, these therapies can also have significant side effects and toxicities, including infections and malignancies. Patients who have progressive disease despite OCS or other immunosuppressive therapy are sometimes given biologic immunomodulators, such as the TNF inhibitors infliximab or adalimumab. These therapies are not approved by the FDA or other regulatory agencies for the treatment of sarcoidosis, and hence providers may face reimbursement challenges if they decide to use these treatments. The clinical efficacy of these agents has not been well established and they are associated with toxicity when used chronically. Given the known toxicities of long-term OCS, immunosuppressive and immunomodulatory biologic therapeutic regimens, treatment of patients with sarcoidosis is limited to those who are symptomatic and whose disease is considered active. The presence of granulomas from sarcoidosis define the disease as active, and granulomatous inflammation is the major cause of fibrosis in pulmonary sarcoidosis. Studies to date have not clearly demonstrated that OCS or other immunomodulatory therapies prevent disease progression or formation of fibrosis. We believe there remains a substantial unmet need for safer, more effective therapies for sarcoidosis that could reduce or replace the requirement for long-term OCS therapy. If efzofitimod is successful for the treatment of pulmonary sarcoidosis, we believe it may have applications in other ILD indications and potentially in other severe forms of inflammatory or fibrotic lung disease. Immunosuppressive therapy has traditionally been used to treat most ILD despite little evidence demonstrating safety or efficacy in these indications. The exception is a specific form of ILD, IPF, where immunosuppressive treatment was demonstrated to be harmful in clinical trials.

We are aware of three FDA approved products with indications for the treatment of a subset of ILD indications. Esbriet (pirfenidone), a pyridine marketed globally by F. Hoffmann-La Roche Ltd., Shionogi & Co., Ltd. and ILDONG Pharmaceutical Co., Ltd., was approved by the FDA in 2014 for the treatment of IPF. Ofev (nintedanib), a small molecule tyrosine-kinase inhibitor marketed globally by Boehringer Ingelheim International GmbH, was approved by the FDA in 2014 for the treatment of IPF. In 2019 Ofev received FDA approval for slowing the rate of decline in pulmonary function in patients with systemic sclerosis-associated ILD (SSc-ILD) and in 2020 the approval was further expanded to include patients with chronic fibrosis ILD with a progressive phenotype. Actemra (tocilizumab), an anti-IL6 antibody marketed globally by F. Hoffmann-La Roche Ltd. and Chugai Pharmaceutical Co Ltd., was approved by the FDA in 2021 for slowing the rate of decline in pulmonary function in adult patients with SSc-ILD. These therapies have been demonstrated the ability to slow decline in lung function as measured by FVC in controlled clinical studies but are associated with significant side effects, continued symptoms, and progressive disease in the majority of patients.

There are a number of companies engaged in the clinical development of potential new treatments for ILD, including Boehringer Ingelheim International GmbH, F. Hoffmann-La Roche Ltd, Novartis Pharmaceuticals Corporation, Galapagos NV, Mallinckrodt plc., Horizon Therapeutics, Xentria, Inc., SarcoMed USA and Kinevant Sciences GmbH among others.

ATYR2810

ATYR2810 is in preclinical development for the potential treatment of certain aggressive cancers where NRP2 is implicated. The primary goal of cancer treatment is to remove the tumor, rid the body of wandering cancer cells, and prevent a recurrence. Pre-clinical evidence suggests that ATYR2810 may present a unique mechanism of action for increasing responsiveness to chemotherapy and preventing metastasis, that may prove complimentary to currently available treatment options and improve patient outcomes.

The commercial and development landscape in oncology is fiercely competitive. There are a number of approved therapies that target different mechanisms driving tumor growth, resistance and metastasis including chemotherapy, radiotherapy, targeted therapy and immunotherapy, with over 70 new initial drug approvals by the FDA since 2015, and over 120 new FDA approval notices (new indications or initial approvals) in the last two years. There are even more potential new therapies in clinical development with over 100 new treatments projected to be approved in the next five years. The majority of major pharmaceutical companies list oncology as a core therapeutic focus area. In addition, there are many specialized oncology focused biotechnology and specialty pharmaceutical companies currently marketing and/or developing a range of cancer therapies. Even though we are not aware of any other companies working on therapeutic approaches specifically targeting the NRP2/VEGF axis, or targeting cancers where NRP2 is implicated, other mechanisms or modalities may prove to be as or more effective, or safer than ATYR2810 in the same indications we are pursuing.

Sales and Marketing

We intend, where strategically appropriate, to build the commercial infrastructure necessary to effectively support the commercialization of our product candidates, if and when we believe a regulatory approval of the first of such product candidates in a particular geographic market appears imminent. We may elect to utilize strategic partners, distributors, or contract sales forces to assist in the commercialization of our product candidates in selected geographic locations or for particular indications. For example, we have licensed the rights to Kyorin to develop and commercialize efzofitimod in Japan.

Additional capabilities important to the marketing of therapeutics include the management of key stakeholders such as managed care organizations, group-purchasing organizations, specialty pharmacies, and government accounts. To develop the appropriate commercial infrastructure, we will have to invest significant amounts of financial and management resources, some of which will be committed prior to any confirmation that any of our product candidates will be approved.

Manufacturing

We currently contract with third parties for the manufacturing and testing of our product candidates, including efzofitimod and ATYR2810, to support preclinical studies and clinical trials, and we intend to do so in the future. We do not own or operate manufacturing or testing facilities for the clinical or commercial production of our product candidates. We currently have no plans to build our own clinical or commercial scale manufacturing capabilities. The use of contracted development and manufacturing organizations (CDMOs), and contract research organizations (CROs), is cost-efficient and has eliminated the need for our direct investment in manufacturing facilities and additional resources early in development. Although we rely on CDMOs and CROs, we employ personnel with extensive biologics development and manufacturing experience to oversee such CDMOs and CROs.

Efzofitimod is a fusion protein that is expressed in recombinant *E.coli* by expression in inclusion bodies and refolding to recreate the native structure. ATYR2810 is recombinant monoclonal antibody to NRP2 that is produced recombinantly in mammalian cells, and then purified using industry standard monoclonal antibody production techniques. We have worked with CDMOs in the United States and internationally on the development and scaled up manufacture of both product candidates using current Good Manufacturing Practices (cGMP) to produce drug substance to support preclinical and clinical development, as well as for the production of drug product. We have also contracted with CROs to conduct the labeling, storage and distribution of our product candidates to clinical sites.

To date, our CDMOs and CROs have met our manufacturing requirements for clinical development and we expect that our current CDMOs and CROs are capable of providing sufficient quantities of our product candidates to meet our anticipated clinical development needs. However, we, and our CDMOs and CROs are currently experiencing delays due to the ongoing COVID-19 pandemic in the delivery of key raw materials which are essential for the production of efzofitimod, the result of which may cause delays and shortfalls in our ability to manufacture sufficient efzofitimod, and other clinical candidates, to meet our projected clinical development needs. Currently we have sufficient efzofitimod on hand to meet our projected needs for the planned registrational trial to be initiated in 2022.

Patents and Proprietary Rights

We strive to protect the proprietary technologies that we believe are important to our business, including seeking and maintaining patent protection intended to cover the composition of matter of our product candidates, their methods of use, related technology and other inventions that are important to our business. We own, or have exclusive licenses to, over 220 issued patents or

allowed patent applications with predicted expiration dates ranging from 2026 to 2034. In addition to patent protection, we also rely on trade secrets and careful monitoring of our proprietary information to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business, defend and enforce our patents, maintain our licenses to use intellectual property owned by third parties, preserve the confidentiality of our trade secrets and operate without infringing the valid and enforceable patents and other proprietary rights of third parties. We also rely on know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen, and maintain our proprietary position in the field of extracellular tRNA synthetase biology, their receptors and associated signaling pathways, including, for example, antibody diagnostics and therapeutics to NRP2.

A third party may hold intellectual property, including patent rights, which is important or necessary to the development of our products. 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 on commercially reasonable terms, or our business could be harmed, possibly materially.

We plan to continue to expand our intellectual property estate by filing patent applications directed to new methods of treatment, therapeutics and additional new product forms thereof with new therapeutic or pharmacokinetic properties. Specifically, we seek patent protection in the United States and internationally for novel compositions of matter covering our protein therapeutics, antibody therapeutics, next generation product forms and the use of these compositions in a variety of therapies.

The patent positions of biopharmaceutical companies like us are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Consequently, we do not know whether any of our product candidates will be protectable or remain protected by enforceable patents. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient proprietary protection from competitors. Any patents that we hold may be challenged, circumvented or invalidated by third parties.

Because patent applications in the United States and certain other jurisdictions are maintained in secrecy for 18 months, and since publication of discoveries in the scientific or patent literature often lags behind actual discoveries, we cannot be certain of the priority of inventions covered by pending patent applications. Moreover, we may have to participate in interference proceedings declared by the United States Patent and Trademark Office (USPTO), or a foreign patent office to determine priority of invention or in post-grant challenge proceedings, such as oppositions, that challenge priority of invention or other features of patentability. Such proceedings could result in us incurring substantial costs, even if the eventual outcome is favorable to us.

Efzofitimod

Our efzofitimod patent portfolio is comprised of a number of patent families related to derivatives of HARS, including the HARS amino 2-60, related splice variants, combinations with other therapeutics, and next-generation product forms with modified therapeutic activity or pharmacokinetic characteristics. As of March 2022, our efzofitimod patent portfolio includes a patent family that is jointly owned by us and our 98% owned subsidiary, Pangu BioPharma, and includes issued patents in the United States, Australia, Canada, China, Europe, Japan and Hong Kong, and pending patent applications in the United States. The U.S. patents are expected to expire between 2030 and 2031, absent any patent term extension for regulatory delays, and the ex-U.S. patents, and patents that issue from these patent applications, if any, are expected to expire in 2030, absent any patent term extension.

The efzofitimod patent portfolio includes another patent family jointly owned by us and Pangu BioPharma, which includes patent applications directed to related splice variants of HARS. This patent family includes issued patents in the United States, Australia, Canada, China, Japan, New Zealand and Hong Kong. The issued patents and any patents that issue from these patent applications, if any, are expected to expire in 2031, absent any patent term extension.

Also included within the efzofitimod patent portfolio are issued patents and pending patent applications directed to specific product forms of efzofitimod, and other HARS splice variants, including patent families directed to Fc fusion proteins, and combinations for treating lung inflammation, among other indications. One family directed to specific Fc fusion proteins includes issued patents in Australia, the United States, Europe, Hong Kong, and Japan, and pending applications in the United States, Canada, China, Hong Kong, India, and Japan. If issued, the patents that derive from the patent applications are predicted to expire between 2034 and 2038, absent any patent term extensions.

ATYR2810 and Discovery NRP2 Antibodies

We filed various US patent applications and corresponding international patent applications under the Patent Cooperation Treaty (PCT) that are directed to our first generation of domain-specific NRP2 antibodies, including affinity-matured and humanized antibodies such as our product candidate ATYR2810, and antibodies that selectively bind to specific splice isoforms of NRP2. Certain of the anti-NRP2 antibodies display preferential functional activity on the VEGF, semaphorin, and other signaling pathways, and form one element of a multilayered approach to develop an anti-NRP2 antibody IP portfolio. Any patents issuing from these patent applications are expected to expire between 2039 and 2040, absent any patent term extension.

tRNA Synthetase

Our pipeline of extracellular tRNA synthetase proteins is covered by a series of patent families, which are directed to all 20 human cytosolic tRNA synthetases. Numerous patents are issued in the United States and elsewhere, including issued U.S. patents directed to specific therapeutic protein compositions, the corresponding protein polynucleotide sequences, and certain antibody compositions to specific splice variants. These cases are jointly owned by us and Pangu BioPharma, and include issued patents and/or pending applications in the United States, Australia, Canada, Europe, China and Japan. Patents that issue from these applications, if any, would be expected to expire in 2031, absent any patent term extension. Additional patent applications have also been separately filed on GARS (Glycyl-tRNA synthetase), DARS, YARS (tyrosyl-tRNA synthetase), and other tRNA synthetases, and any patents issuing from these patent applications are expected to expire between 2026 and 2030, absent any patent term extension.

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

In the United States, the patent term of a patent that covers a drug approved by the FDA, may also be eligible for patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. Patent extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Similar provisions are available in Europe and other non-United States jurisdictions to extend the term of a patent that covers an approved drug. In the future, if and when our pharmaceutical products receive FDA approval, we expect to apply for patent term extensions on patents covering those products. We intend to seek patent term extensions to any of our issued patents in any jurisdiction where these are available, however there is no guarantee that the applicable authorities, including the FDA in the United States, will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such extensions.

We also rely on trade secret protection for our confidential and proprietary information. Although we take steps to protect our proprietary information and trade secrets, including through contractual means with our employees and consultants, third parties may independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or disclose our technology. Thus, we may not be able to meaningfully protect our trade secrets. It is our policy to require our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors to execute confidentiality agreements upon the commencement of employment or consulting relationships with us. These agreements provide that all confidential information concerning our business or financial affairs developed or made known to the individual during the course of the individual's relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. In the case of employees, the agreements provide that all inventions conceived by the individual, and which are related to our current or planned business or research and development or made during normal working hours, on our premises or using our equipment or proprietary information, are our exclusive property.

Government Regulation

Government authorities in the United States, including federal, state, and local authorities, and in other countries, extensively regulate, among other things, the manufacturing, research and clinical development, marketing, labeling and packaging, storage, distribution, post-approval monitoring and reporting, advertising and promotion, and export and import of biological products, such as those we are developing. Pricing of such products is also subject to regulation in many countries. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local, and foreign statutes and regulations require the expenditure of substantial time and financial resources.

U.S. Government Regulation

In the United States, the FDA regulates biologics under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act and their implementing regulations. FDA approval is required before any new unapproved biologic or dosage form, including a new use of a previously approved biologic, can be marketed in the United States. Biologics are also subject to other

federal, state, and local statutes and regulations. If we fail to comply with applicable FDA or other requirements at any time during the product development process, clinical testing, approval process or after approval, we may become subject to administrative or judicial sanctions. These sanctions could include the FDA's refusal to approve pending applications, license suspension or revocation, untitled or warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties or criminal prosecution. Any FDA enforcement action could have a material adverse effect on us.

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

- completion of extensive preclinical laboratory tests and preclinical animal studies, performed in accordance with the good laboratory practice regulations, where applicable;
- submission to the FDA of an IND which must become effective before human clinical trials may begin and must be updated annually;
- approval by an independent institutional review board (IRB) or ethics committee representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials to establish the safety and efficacy of the product candidate for each proposed indication and conducted in accordance with good clinical practice (GCP) requirements;
- preparation of and submission to the FDA of a biologics license application (BLA) after completion of all pivotal clinical trials;
- potential review of the product application by an FDA advisory committee, where appropriate and if applicable;
- a determination by the FDA within 60 days of its receipt of a BLA to file the application for review;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facilities where the proposed product is produced to assess compliance with cGMP;
- potential FDA audit of the clinical trial sites that generated the data in support of the BLA; and
- FDA review and approval of a BLA prior to any commercial marketing or sale of the product in the United States.

The preclinical and clinical testing and approval process requires substantial time, effort, and financial resources, and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all.

An IND is a request for authorization from the FDA to administer an investigational new drug or biologic product to humans in clinical trials. The IND submission includes the general investigational plan and the protocol(s) for human trials. The IND also includes results of preclinical testing, including animal and *in vitro* studies, to assess the toxicology, PK, 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 new drug. An IND must become effective before human clinical trials may begin. An IND will automatically become effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to the proposed clinical trials. 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 clinical trials can begin. Accordingly, submission of an IND may or may not result in the FDA allowing clinical trials to commence. The FDA may impose a clinical hold at any time during a clinical trial and may impose a partial clinical hold that would apply certain limits to the trial, for example, imposing dosage limitations or restricting the time frame of the 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 GCPs which include the requirement that all research subjects provide their informed consent for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety, and the efficacy 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. Additionally, approval must also be obtained from each clinical trial site's IRB before the trials may be initiated, and the IRB must monitor the trial until it is completed. There are also requirements governing the reporting of ongoing clinical trials and clinical trial results to public registries.

The clinical investigation of a drug is generally divided into three phases. Although the phases are usually conducted sequentially, they may overlap or be combined.

- Phase 1. The drug is initially introduced into a relatively small number of healthy human subjects or patients with the target disease or condition. These studies are designed to evaluate the safety, dosage tolerance, metabolism and pharmacologic actions of the investigational new drug in humans, the side effects associated with increasing doses, and if possible, to gain early evidence on effectiveness.
- Phase 2. The drug is administered to a limited patient population to evaluate dosage tolerance and optimal dosage, identify possible adverse side effects and safety risks, and preliminarily evaluate efficacy. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more costly Phase 3 clinical trials.
- Phase 3. The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites to generate enough data to evaluate dosage, clinical effectiveness and safety, and establish the overall benefit-risk relationship of the investigational new drug product. A well-controlled, statistically robust Phase 3 trial may be designed to deliver the data that regulatory authorities will use to decide whether or not to approve, and, if approved, how to appropriately label a drug: such Phase 3 studies are referred to as “pivotal.”

In some cases, the FDA may condition approval of a BLA for a product candidate on the sponsor’s agreement to conduct additional clinical trials after approval. In other cases, a sponsor may voluntarily conduct additional clinical trials after approval to gain more information about the drug. Such post-approval studies are typically referred to as Phase 4 clinical trials. Failure to exhibit due diligence with regard to conducting Phase 4 clinical trials that the FDA requires as a condition of approval could result in FDA withdrawing approval for the product.

A clinical trial sponsor must submit written IND safety reports to the FDA and the investigators for serious and unexpected adverse reactions, any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator’s brochure, or any findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the product candidate within 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor’s initial receipt of the information. The FDA, the IRB, or the clinical trial sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a trial may move forward at designated check points based on access to certain data from the trial. We may also suspend or terminate a clinical trial based on evolving business objectives or competitive climate.

BLA Submission

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, detailed information about the investigational biologic product is submitted to the FDA in the form of a BLA requesting approval to market the product for one or more indications. Efzofitimod, ATYR2810 and our other potential product candidates are proteins that will be regulated as biological products subject to the BLA marketing pathway. Under federal law, the submission of most BLAs is subject to an application user fee, and the sponsor of an approved BLA is also subject to an annual prescription drug product program fee. These fees typically increase annually. Applications for orphan drug products are exempted from the BLA user fees, unless the application includes an indication for other than a rare disease or condition.

A BLA must include all relevant data available from pertinent preclinical studies and clinical trials, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product’s chemistry, manufacturing, controls, and proposed labeling, among other things. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and effectiveness of the investigational new drug product to the satisfaction of the FDA. FDA approval of a BLA must be obtained before a biologic may be marketed in the United States.

Before approving a BLA, the FDA typically will conduct a pre-approval inspection of 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 a BLA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP.

Additionally, the FDA may refer any NDA or BLA, including applications for novel biologic candidates which present difficult questions of safety or efficacy, to an advisory committee. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

The FDA's Decision on a BLA

The FDA evaluates a BLA to determine whether the data demonstrate that the biologic is safe, pure, and potent, or effective. After the FDA evaluates the BLA and conducts inspections of manufacturing facilities where the product will be produced, it may issue an approval letter or a Complete Response Letter (CRL). An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. A CRL indicates that the review cycle of the application is complete and the application is not ready for approval. A CRL generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. A CRL may require additional clinical data or an additional pivotal Phase 3 clinical trial(s), or other significant, expensive and time-consuming requirements related to clinical trials, preclinical studies or manufacturing. Even with the submission of this additional information, however, the FDA may ultimately decide that the BLA does not satisfy the criteria for approval and issue a denial.

The FDA could also approve the BLA with a Risk Evaluation and Mitigation Strategy plan to mitigate risks associated with the product, 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. The FDA may also condition approval on, among other things, changes to proposed labeling, development of adequate controls and specifications, or a commitment to conduct one or more post-market studies or clinical trials. Such post-market testing may include Phase 4 clinical trials and surveillance to further assess and monitor the product's safety and effectiveness after commercialization. Also, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our products under development.

Expedited Review and Accelerated Approval Programs

A sponsor may seek approval of its product candidate under programs designed to accelerate FDA's review and approval of NDAs and BLAs. For example, fast track designation may be granted to a drug or biologic intended for treatment of a serious or life-threatening disease or condition that has potential to address unmet medical needs for the disease or condition by providing a therapy where none exists or a therapy that may be potentially superior to existing therapy based on efficacy or safety factors. The key benefits of fast track designation are more frequent interactions with the FDA during development and testing and eligibility for priority review. The FDA may also review sections of the NDA or BLA for a fast track product on a rolling basis before the complete application is submitted, if the sponsor and the FDA agree on a schedule for the submission of the application sections, and the sponsor pays any required user fees upon submission of the first section of the application. Based on results of the Phase 3 clinical trial(s) submitted in a BLA, the FDA may grant the BLA a priority review designation, which sets the target date for FDA action on the application at six months after the FDA accepts the application for filing. Priority review is granted where there is evidence that the proposed product would be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition. If criteria are not met for priority review, the application 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. 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.

Under the accelerated approval program, the FDA may approve a BLA on the basis of either a surrogate endpoint that is reasonably likely to predict clinical benefit or, on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Drugs and biologics granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval. Post-marketing trials or completion of ongoing trials after marketing approval are generally required to verify the drug's clinical benefit in relationship to the surrogate endpoint or ultimate outcome in relationship to the clinical benefit. In addition, a sponsor may seek FDA designation of its product candidate as a breakthrough therapy if the drug is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. If so designated, the FDA shall act to expedite the development and review of the product's marketing application, including by meeting with the sponsor throughout the product's development, providing timely advice to the sponsor to ensure that the development program to gather preclinical and clinical data is as efficient as practicable, involving senior managers and experienced review staff in a cross-disciplinary review, and 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.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved

product, such as adding new indications or other labeling claims or some changes to the manufacturing process, are subject to prior FDA review and approval.

Drug manufacturers are subject to periodic unannounced inspections by the FDA and state agencies for compliance with cGMP requirements.

We rely, and expect to continue to rely, on third parties for the production of clinical quantities of our product candidates, and expect to rely in the future on third parties for the production of commercial quantities. Future FDA and state inspections may identify compliance issues at our facilities or at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct. In addition, discovery of previously unknown problems with a product or the failure to comply with applicable requirements may result in restrictions on a product, manufacturer or holder of an approved BLA, including withdrawal or recall of the product from the market or other voluntary, FDA-initiated or judicial action that could delay or prohibit further marketing, or result in the imposition of post-market studies or trials to assess new safety risks.

The FDA strictly regulates marketing, labeling, advertising, and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

Orphan Designation and Exclusivity

The FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the United States, or if it affects more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making a drug for this type of disease or condition will be recovered from sales in the United States. Orphan drug designation must be requested before submitting an NDA or BLA. After the FDA grants orphan drug designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA.

In January 2022, the FDA granted efzofitimod an orphan drug designation for the treatment of sarcoidosis.

Orphan drug designation does not convey any advantage in or shorten the duration of the regulatory review and approval process, but it entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages, and user-fee waivers. In addition, if a product is the first to receive FDA approval for the indication for which it has orphan designation, the product is entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity. Orphan drug exclusivity, however, also could block the approval of one of our products for seven years if a competitor obtains approval of the same drug as defined by the FDA for treatment of the same indication or disease.

Pediatric Trials and Exclusivity

Under the Pediatric Research Equity Act of 2003, as amended, BLAs or supplement to a BLA must contain data that are adequate to assess the safety and effectiveness of an investigational drug or biologic product for the claimed indications in all relevant pediatric populations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. A sponsor who is planning to submit a marketing application for a drug product that includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration must submit an initial Pediatric Study Plan (PSP) within sixty days of an end-of-phase 2 meeting or, if there is no such meeting, as early as practicable before the initiation of the Phase 3 or Phase 2/3 clinical trial. The initial PSP must include an outline of the pediatric study or studies that the sponsor plans to conduct, including study objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information. 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 if certain criteria are met. The FDA and the sponsor must reach agreement on the PSP. A sponsor can submit amendments to an agreed-upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from preclinical studies, early phase clinical trials, and/or other clinical development programs. The requirements for pediatric data do not apply to any drug or biologic for an indication for which orphan designation has been granted, except under certain circumstances.

Pediatric exclusivity is another type of non-patent exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including orphan exclusivity. This six-month exclusivity may be granted if a BLA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data.

Rest of World Government Regulation

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of our products. The cost of establishing a regulatory compliance system for numerous varying jurisdictions can be very significant. Although many of the issues discussed above with respect to the United States apply similarly in the context of the European Union and in other jurisdictions, the approval process varies between countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials. In the EU, for example, a clinical trial authorization application (CTA) must be submitted for each clinical protocol to each country's national health authority and an independent ethics committee, much like the FDA and IRB, respectively. Once the CTA is accepted in accordance with a country's requirements, the clinical trial may proceed.

The requirements and process governing the conduct of clinical trials vary from country to country. In all cases, the clinical trials are conducted in accordance with GCP the applicable regulatory requirements, and the ethical principles that have their origin in the Declaration of Helsinki.

Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any products for which we obtain regulatory approval. In the United States and in other countries, sales of any products for which we receive regulatory approval for commercial sale will depend in part on the availability of coverage and reimbursement from third-party payors. Third-party payors include government authorities, managed care providers, private health insurers and other organizations. Private payors often follow Centers for Medicare & Medicaid Services (CMS's) determinations relating to Medicare and Medicaid with respect to coverage policy and payment limitations in setting their own reimbursement policies. 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. Third-party payors may 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. Moreover, a payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available or sufficient to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. In order to obtain 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 regulatory approvals. Our product candidates may 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.

The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid health care costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. By way of example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010 (collectively, the ACA) contains provisions that may reduce the profitability of drug products, including, for example, increased rebates for drugs sold to Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies' share of sales to federal health care programs. There have been executive, judicial and Congressional challenges to certain aspects of the ACA. For example, legislation enacted in 2017, informally titled the Tax Cuts and Jobs Act of 2017, included a provision which repealed, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." On June 17, 2021, the Supreme Court dismissed a challenge on procedural grounds that argued the ACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. Thus, the ACA will remain in effect in its current form.

Prior to the Supreme Court ruling, on January 28, 2021, President Biden issued an executive order to initiate 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 any such challenges and the healthcare reform measures of the Biden administration will impact the ACA and our business.

In addition, there 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 congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. For example, on July 24, 2020 and September 13, 2020, President Trump announced several executive orders related to prescription drug pricing that attempted to implement several of the Administration's proposals. The FDA concurrently released a final rule and guidance in September 2020 implementing a portion of the importation executive order providing pathways for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020, the U.S. Department of Health and Human Services (HHS) finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of the rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which have also been delayed by the Biden administration until January 1, 2023. On November 20, 2020, CMS issued an interim final rule implementing President Trump's Most Favored Nation executive order, which would tie Medicare Part B payments for certain physician-administered drugs to the lowest price paid in other economically advanced countries, effective January 1, 2021. As a result of litigation challenging the Most Favored Nation model, on December 27, 2021, CMS published a final rule that rescinds the Most Favored Nation model interim final rule. Additionally, 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 as well as potential administrative actions HHS can take to advance these principles. No legislation or administrative actions have been finalized to implement these principles. It is unclear whether these or similar policy initiatives will be implemented in the future. Congress is also considering additional health reform measures. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. Additional state and federal healthcare reform measures may be adopted in the future. Further, it is possible that additional governmental action is taken in response to the ongoing COVID-19 pandemic.

In the European Community, governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed to by the government. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular product candidate to currently available therapies. Other member states allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on health care 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. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, an increasing emphasis on cost containment measures in the United States and other countries has increased and we expect will continue to increase the pressure on pharmaceutical pricing. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Other Healthcare Laws and Compliance Requirements

If we obtain regulatory approval for any of our product candidates, we may be subject to various federal and state laws targeting fraud and abuse in the healthcare industry. These laws may impact, among other things, our proposed sales, marketing and education programs. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce, or in return for, the purchase or

recommendation of an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs;

- federal civil and criminal false claims laws and civil monetary penalty laws, including the civil False Claims Act, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payors that are false or fraudulent;
- the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA), which created new federal criminal statutes that prohibit executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;
- the federal transparency laws, including the provision of the ACA referred to as the federal Physician Payments Sunshine Act, that requires certain drug and biologics manufacturers to disclose payments and other transfers of value provided to physicians (defined to include doctors, dentists, optometrists, podiatrists, and chiropractors), certain other healthcare professionals (such as physician assistants and nurse practitioners), and teaching hospitals and ownership interests of physicians and their immediate family members;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, which imposes certain requirements on HIPAA covered entities and their business associates relating to the privacy, security and transmission of individually identifiable health information; and
- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws that may apply to items or services reimbursed by any third-party payor, including commercial insurers, and state laws governing transparency, marketing and drug pricing reporting, and the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

The ACA broadened the reach of the fraud and abuse laws by, among other things, amending the intent requirement of the federal Anti-Kickback Statute and certain other criminal healthcare fraud statutes. Pursuant to the statutory amendment, a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the ACA provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act or the civil monetary penalties statute. Many states have adopted laws similar to the federal Anti-Kickback Statute, some of which apply to the referral of patients for healthcare items or services reimbursed by any source, not only the Medicare and Medicaid programs.

We are also subject to the U.S. Foreign Corrupt Practices Act (FCPA), which prohibits improper payments or offers of payments to foreign governments and their officials for the purpose of obtaining or retaining business. Safeguards we implement to discourage improper payments or offers of payments by our employees, consultants, and others may be ineffective, and violations of the FCPA and similar laws may result in severe criminal or civil sanctions, or other liabilities or proceedings against us, any of which would likely harm our reputation, business, financial condition and result of operations.

If our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including significant administrative, civil and criminal penalties, exclusion from participation in government healthcare programs, such as Medicare and Medicaid and imprisonment, disgorgement, damages, fines, additional reporting requirements and regulatory oversight and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

Employees and Human Capital Resources

As of December 31, 2021, we had 53 employees, 49 of which were full-time employees. 32 of our employees serve in roles related to research and development, clinical, manufacturing and regulatory affairs, and 17 serve in general and administrative capacities. As of December 31, 2021, all our employees were based in the United States. We also engage temporary consultants and contractors. All of our employees are “at–will,” which means that each employee can terminate his or her relationship with us and we can terminate our relationship with him or her, at any time. None of our employees are represented by a labor union or covered by collective bargaining agreements. We consider our relationship with our employees to be good.

We compete in the highly competitive biotechnology industry. Attracting, developing and retaining talented employees is crucial to executing our strategy and our ability to compete effectively. Our ability to recruit and retain such talent depends on several factors, including compensation and benefits, talent development and career opportunities, and work environment. To that end, we invest in our employees to be an employer of choice.

Our Code of Business Conduct and Ethics (Code of Conduct) ensures that our core values of respect, integrity, collaboration, innovation, trust, and excellence are applied throughout our operations. Our Code of Conduct serves as a critical tool to help all of us recognize and report unethical conduct, while preserving and nurturing our culture of honesty and accountability.

The physical health, financial wellbeing, work-life balance and mental health of our employees is vital to our success. Our environmental, health and safety team stays abreast of local, regional and global concerns and trends and ensures safety procedures are in place to mitigate workplace injuries and safety risks. Our employees are required to complete training in various safety procedures for the laboratories and manufacturing facilities and specialized safety training based on particular job duties. Our Designated Safety Officers and response teams oversee safety-related initiatives and a safety committee that provides input on safety procedures, practices, and policies. Our employees are required to wear personal protective equipment relevant for their particular job duties. Occupational injuries at our facilities are extremely low and are always investigated to determine if any environmental or other changes need to be implemented.

Since the onset of the COVID-19 pandemic, strict safety protocols have been put in place for employees working on-site, including following federal and local guidelines and mandates to ensure the safety of our workforce. We provide the necessary personal protective equipment who are working in our facility. Regular communication and training about the virus and how individuals can protect themselves and others is ongoing with employees.

Financial Information about Segments

We operate in a single accounting segment. Refer to Note 1 to our consolidated financial statements included elsewhere in this Annual Report.

Corporate Information

We were incorporated under the laws of the State of Delaware in September 2005. Our principal executive office is located at 3545 John Hopkins Court, Suite #250, San Diego, California 92121, and our telephone number is (858) 731-8389. Our website address is www.atyrpharma.com.

You are advised to read this Annual Report in conjunction with other reports and documents that we file from time to time with the SEC. Our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, and amendments to these reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act, are available free of charge on our website as soon as reasonably practicable after such reports and amendments are electronically filed with, or furnished to, the SEC. You may obtain copies of these reports directly from us or from the SEC. In addition, the SEC maintains information for electronic filers (including aTyr Pharma, Inc.) at its website at www.sec.gov. We also make available copies of our news releases and other financial information and updates with respect to our business on our website. We do not incorporate the information on or accessible through our website into this Annual Report, and you should not consider any information on, or that can be accessed through, our website as part of this Annual Report.

Item 1A. Risk Factors

You should carefully consider the following risk factors, as well as the other information in this Annual Report on Form 10-K (Annual Report) and in our other public filings with the SEC. The occurrence of any of these risks could harm our business, financial condition, results of operations and/or growth prospects or cause our actual results to differ materially from those contained in forward-looking statements we have made in this Annual Report and those we may make from time to time. You should consider all of the risk factors described in our public filings when evaluating our business.

Risks related to our financial condition and need for additional capital

We will need to raise additional capital or enter into strategic partnering relationships to fund our operations.

The development of therapeutic product candidates is expensive, and we expect our research and development expenses to fluctuate. As of December 31, 2021, our cash, cash equivalents and available-for-sale investments were approximately $107.9 million. We believe that our current cash, cash equivalents and available-for-sale investments, will be sufficient to meet our material cash requirements for known contractual and other obligations for a period of at least one year from the date of this Annual Report. However, our operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through equity or debt offerings, grant funding, collaborations, strategic partnerships and/or licensing arrangements. Our future funding requirements will depend on many factors, including but not limited to:

- our ability to initiate, and the progress and results of, our future clinical trials of efzofitimod (the non-proprietary name for ATYR1923, our lead therapeutic candidate) and ATYR2810;

- the outcome of our planned meetings with the U.S. Food and Drug Administration (FDA) with respect to the design of additional clinical trials of efzofitimod and other registration requirements;
- the costs, timing and outcome of regulatory review of our product candidates;
- our ability to initiate a clinical trial, and the progress and results of, our preclinical program for ATYR2810;
- delays of our planned clinical trials of efzofitimod and ATYR2810 and any resulting cost increases as a result of the ongoing COVID-19 pandemic;
- the number and characteristics of product candidates that we pursue;
- the scope, progress, results and costs of preclinical development, and clinical trials for other product candidates;
- the manufacturing of preclinical study and clinical trial materials, including technology transfers to additional contract development and manufacturing organizations (CDMO), and any delays in the manufacturing of study drug as a result of the ongoing COVID-19 pandemic;
- our ability to maintain existing and enter into new collaboration and licensing arrangements and the timing of any payments we may receive under such arrangements;
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims;
- the costs and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution, for any of our product candidates for which we receive marketing approval; and
- the extent to which we acquire or in-license other products and technologies.

In any event, we will require additional capital to complete additional clinical trials, including larger, pivotal clinical trials, to obtain regulatory approval for, and to commercialize, our product candidates.

Raising funds in the current and future economic environment may present additional challenges. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic considerations. If we are unable to obtain funding on a timely basis, we may be required to significantly curtail, delay or discontinue one or more of our research or development programs or the commercialization of any product candidates, or we may be unable to expand our operations, maintain our current organization and employee base or otherwise capitalize on our business opportunities, as desired, which could materially affect our business, financial condition and results of operations.

The terms of any financing may adversely affect the holdings or the rights of our stockholders and the issuance of additional securities by us, or the possibility of such issuance, may cause the market price of our shares to decline. The sale of additional equity or convertible securities would cause dilution to all of our stockholders. The incurrence of indebtedness would result in fixed payment obligations and may require us to agree to certain restrictive covenants, such as limitations on our ability to incur debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. As a result of the ongoing COVID-19 pandemic, the global credit and financial markets have experienced volatility and disruptions, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates, inflation and uncertainty about economic stability. If the equity and credit markets deteriorate, it may make any necessary debt or equity financing more difficult, more costly and more dilutive. In addition, any fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates.

We may decide to enter into additional strategic partnerships, including collaborations with pharmaceutical and biotechnology companies, to enhance and accelerate the development and potential commercialization of our product candidates. We face significant competition in seeking appropriate partners, and the negotiation process is time-consuming and complex. Moreover, we may not be successful in our efforts to establish any new strategic partnership or other collaborative arrangement for any of our product candidates and programs for a variety of reasons, including strategic fit with partners and differences in analysis of commercial value and regulatory risk. We may not be able to negotiate strategic partnerships on a timely basis, on acceptable terms or at all. We are unable to predict when, if ever, we will enter into any new strategic partnership because of the numerous risks and uncertainties associated with establishing strategic partnerships. Even if we are successful in our efforts to establish new strategic partnerships, the terms that we agree upon may not be favorable to us and we may not be able to maintain such strategic partnerships if, for example, we encounter unfavorable results or delays during development or approval of a product candidate or sales of an approved product are lower than expectations.

We are a pre-commercial biotherapeutics company and have incurred significant losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future.

We are a pre-commercial biotherapeutics company, and we have not yet generated any revenues from product sales. We have incurred net losses in each year since our inception in 2005, including consolidated net losses of $33.8 million, $16.2 million and $23.8 million for the years ended December 31, 2021, 2020 and 2019, respectively. As of December 31, 2021, we had an accumulated deficit of $372.3 million.

We have devoted most of our financial resources to research and development, including our clinical and preclinical development activities. To date, we have financed our operations primarily through the sale of equity securities and convertible debt and through venture debt and term loans. The amount of our future net losses will depend, in part, on the rate of our future expenditures and our ability to obtain funding through equity offerings, grant funding, collaborations, strategic partnerships and/or licensing arrangements. While we intend to initiate a planned registrational trial for efzofitimod in the third quarter of 2022, we have not commenced registrational clinical trials for any product candidate to date and it will be several years, if ever, before we have a product candidate ready for commercialization. Even if we obtain regulatory approval to market a product candidate, our future revenues will depend, in part, upon the size of any markets in which our product candidates have received approval, and our ability to achieve sufficient market acceptance, reimbursement from third-party payors and adequate market share for our product candidates in those markets.

We expect to continue to incur significant expenses and operating losses for the foreseeable future. We anticipate that our expenses will fluctuate in connection with our ongoing activities as we: continue our research and preclinical and clinical development of efzofitimod and ATYR2810 or any other product candidates that we may develop; obtain clinical trial materials and further develop the manufacturing process for our product candidates; seek regulatory approvals for our product candidates that successfully complete clinical trials; ultimately establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval; seek to identify and validate additional product candidates; maintain, protect and expand our intellectual property portfolio; acquire or in-license other product candidates and technologies; attract and retain skilled personnel; and create additional infrastructure to support our operations as a public company and our product development and planned future commercialization efforts.

Our revenues, expenses and income or losses may fluctuate significantly from quarter to quarter and year to year, such that a period-to-period comparison of our results of operations may not be a good indication of our future performance. In any particular quarter or quarters, our operating results could be below the expectations of securities analysts or investors, which could cause our stock price to decline.

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

Our ability to generate revenue and achieve profitability depends on our ability, alone or with strategic collaboration partners, to successfully complete the development of, and obtain the regulatory approvals necessary to commercialize our product candidates. We do not anticipate generating revenues from product sales for the foreseeable future, if ever. Our ability to generate future revenues from product sales depends heavily on our success in:

- completing research, preclinical development and clinical development of our product candidates, potentially with a strategic partner;
- seeking and obtaining regulatory approvals for product candidates for which we complete clinical trials;
- developing a sustainable, scalable, reproducible, and transferable manufacturing process for our product candidates and establishing supply and manufacturing relationships with third parties;
- launching and commercializing product candidates for which we obtain regulatory approval, either by collaborating with a partner or, if launched independently, by establishing a sales force, marketing and distribution infrastructure;
- maintaining, protecting and expanding our intellectual property portfolio;
- obtaining market acceptance of our product candidates as viable treatment options for our target indications;
- identifying and validating new therapeutic product candidates based on tRNA synthetase biology or neuropilin-2 (NRP2) biology, including through our AARS and DARS discovery programs;
- attracting, hiring and retaining qualified personnel; and
- negotiating favorable terms in any licensing, collaboration or other arrangements into which we may enter.

Even if one of our product candidates is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any such approved product candidate. Our expenses could increase beyond expectations if we are required by the FDA or other regulatory agencies, domestic or foreign, to perform clinical trials and other studies in addition to those that we currently anticipate. Even if we are able to generate revenues from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations.

Risks related to the discovery, development and regulation of our product candidates

We may encounter substantial delays and other challenges in our planned clinical trials or we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidates in humans. Clinical trials are expensive, time-consuming, often delayed and uncertain as to outcome. We cannot guarantee that future trials we may plan to conduct, will be initiated or conducted as planned or completed on schedule, if at all. We cannot assure you that our product candidates will not be subject to new clinical holds or significant delay in the future. For example, in our Phase 1b/2a clinical trial of efzofitimod in patients with pulmonary sarcoidosis, FDG-PET/CT was not evaluable due to incomplete data primarily caused by operational issues related to the ongoing COVID-19 pandemic. Any inability to initiate or complete clinical trials of our product candidates in the United States, as a result of clinical holds or otherwise, would delay our clinical development plans, may require us to incur additional clinical development costs and could impair our ability to obtain U.S. regulatory approval for such product candidates.

A failure of one or more clinical trials can occur at any stage of testing, and our clinical trials may not be successful. Events that may prevent successful or timely completion of clinical development include, but are not limited to:

- our inability to generate sufficient preclinical, toxicology, or other *in vivo* or *in vitro* data to support the initiation of human clinical trials, including trials of certain dosages;
- delays in reaching consensus with regulatory agencies on trial design, including with respect to the endpoints for our planned registrational study of efzofitimod and prioritization of outcome measurements that would best support the evaluation of efzofitimod's efficacy;
- delays in reaching agreement on acceptable terms with prospective clinical contract research organizations (CROs) and clinical trial sites;
- delays in obtaining required institutional review board or Ethics Committee approval at each clinical trial site;
- delays in recruiting suitable patients to participate in our clinical trials, or delays that may result if the number of patients required for a clinical trial is larger than we anticipate;
- imposition of a clinical hold by regulatory agencies, which may occur at any time before or during a clinical trial, including after our submission of data to these agencies or an inspection of our clinical trial operations or trial sites;
- failure by our CROs, investigators, other third parties or us to adhere to clinical trial requirements;
- failure to perform in accordance with the FDA's good clinical practices (GCPs) or applicable regulatory requirements in other countries;
- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites;
- delays in having patients complete participation in a trial or return for post-treatment follow-up;
- disagreements with regulators regarding our interpretation of data from preclinical studies or clinical trials;
- occurrence of adverse events associated with a product candidate that are viewed to outweigh its potential benefits; or
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols.

Any delay in or inability to successfully complete preclinical and clinical development could result in additional costs to us and impair our ability to generate revenue. In addition, if we make manufacturing or formulation changes to our product candidates (including our planned technology transfer to another CDMO for bulk drug substance and production capacity changes for efzofitimod), we may need to conduct additional studies to bridge our modified product candidates to earlier versions.

If the results of our future clinical trials are perceived to be negative or inconclusive, or if there are safety concerns or adverse events associated with our product candidates, we may be required to perform additional clinical trials to support approval or be subject to additional post-marketing testing requirements; be delayed in obtaining marketing approval for our product candidates, if at all; obtain approval for indications or patient populations that are not as broad as intended or desired; obtain approval with labeling that includes significant use or distribution restrictions or safety warnings; be subject to changes in the way the product is

manufactured or administered; have regulatory authorities withdraw their approval of the product or impose restrictions on its distribution in the form of a modified risk evaluation and mitigation strategy; be subject to litigation; or experience damage to our reputation.

To date, the safety and efficacy of efzofitimod has only been studied in a limited number of humans and ATYR2810 has not been studied in humans at all. Accordingly, efzofitimod, ATYR2810 and any future product candidates could potentially cause unexpected adverse events. In addition, the inclusion of critically ill patients in our clinical trials may result in deaths or other adverse medical events due to the natural progression of the disease.

Further, if patients drop out of any future trials, miss scheduled doses or follow-up visits or otherwise fail to follow trial protocols, or if our trials are otherwise disrupted due to the ongoing COVID-19 pandemic or actions taken to slow its spread, the integrity of data from our trials may be compromised or not accepted by the FDA or other regulatory authorities, which would represent a significant setback for the applicable program. In addition, the ongoing COVID-19 pandemic has impacted clinical trials broadly, including our efzofitimod Phase 1b/2a trial in patients with pulmonary sarcoidosis, where many sites stopped enrollment and patients chose not to enroll or continue participating in the trial. While we completed the clinical trial, the availability of results from the Phase 1b/2a clinical trial was delayed to September 2021. We may experience delays in site initiation and patient enrollment, failures to comply with study protocols, delays in the manufacture of study drug for clinical testing and other difficulties in starting or completing our future trials due to the ongoing COVID-19 pandemic, including the emergence of new variants of COVID-19.

Interim, top-line 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 top-line data from our clinical studies, which are based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data 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 top-line 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. Top-line data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, top-line data should be viewed with caution until the final data are available. From time to time, we may also disclose interim data from our clinical studies.

In addition, we may report interim analyses of only certain endpoints rather than all endpoints. 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. 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 a 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, and any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise regarding a particular product, product candidate or our business. If the top-line 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.

If we are unable to successfully complete or otherwise advance clinical development, obtain regulatory or marketing approval for, or successfully commercialize our therapeutic product candidates, including efzofitimod and ATYR2810, or experience significant delays in doing so, our business will be materially harmed.

To date, we have expended significant time, resources and effort on the discovery and development of product candidates related to the extracellular proteins derived from the histidyl tRNA synthetase (HARS) family and NRP2 biology, including conducting preclinical studies and clinical trials. We have not yet commenced or completed any evaluation of our product candidates in human clinical trials designed to demonstrate efficacy to the satisfaction of the FDA. Before we can market or sell our therapeutic candidates in the United States or foreign jurisdictions, we will need to commence and complete additional clinical trials (including larger, pivotal trials, which we have not yet commenced), manage clinical and manufacturing activities, obtain necessary regulatory approvals from the FDA in the United States and from similar regulatory authorities in other jurisdictions, obtain adequate clinical and

commercial manufacturing supplies, build commercial capabilities, which may include entering into a marketing collaboration with a third party, and in some jurisdictions, obtain reimbursement authorization, among other things. We cannot assure you that we will be able to successfully complete the necessary clinical trials, obtain regulatory approvals, secure an adequate commercial supply for, or otherwise successfully commercialize our therapeutic candidates. If we do not receive regulatory approvals for our product candidates, and even if we do obtain regulatory approvals, we may never generate significant revenues, if any, from commercial sales. If we fail to successfully commercialize our therapeutic candidates, we may be unable to generate sufficient revenues to sustain and grow our company, and our business, prospects, financial condition and results of operations will be adversely affected.

We have encountered and may continue to encounter delays and difficulties enrolling patients in our clinical trials for a variety of reasons, including the limited number of patients who have the diseases for which certain of our product candidates are being studied, which could delay or halt the clinical development of our product candidates.

Identifying and qualifying patients to participate in clinical trials for our product candidates is critical to our success. Certain of the conditions for which we may elect to evaluate our product candidates may be rare diseases with limited patient pools from which to draw for clinical trials.

For example, we are currently planning our next efzofitimod clinical trial in patients with pulmonary sarcoidosis, and we intend to initiate this planned registrational trial in the third quarter of 2022. While estimates of pulmonary sarcoidosis prevalence vary, we estimate that pulmonary sarcoidosis affects an estimated 200,000 patients in the United States. Of that population, however, we estimate that approximately 30% experience progressive disease such that our targeted population is significantly smaller. The eligibility criteria for any of our future clinical trials may further limit the pool of available participants in our trials. We may be unable to identify and enroll a sufficient number of patients with the disease in question and who meet the eligibility criteria for, and are willing to participate in, the clinical trials. Once enrolled, patients may decide or be required to discontinue from the clinical trial due to inconvenience, burden of trial requirements, adverse events associated with efzofitimod, limitations required by trial protocols or other reasons.

Our ability to identify, recruit, enroll and maintain a sufficient number of patients, or those with required or desired characteristics to achieve diversity in future clinical trials in a timely manner may also be affected by other factors, including, but not limited to:

- proximity and availability of clinical trial sites for patients;
- severity of the disease under investigation;
- design of the study protocol and the burdens to patients of compliance with our study protocol;
- perceived risks and benefits of the product candidate under study;
- availability of competing therapies and clinical trials for the patient populations and indications under study;
- efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians; and
- ability to monitor patients adequately during and after treatment.

We plan to seek initial marketing approval in the United States. We may not be able to initiate or continue clinical trials if we cannot enroll a sufficient number of eligible patients to participate in the clinical trials required by the FDA or other regulatory agencies. Our ability to successfully initiate, enroll and complete a clinical trial in any foreign country is subject to numerous risks unique to conducting business in foreign countries, including, but not limited to:

- difficulty in establishing or managing relationships with CROs and physicians;
- different requirements and standards for the conduct of clinical trials;
- our inability to locate qualified local consultants, physicians and partners; and
- the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of biotechnology products and treatment.

Additionally, if patients are unwilling to participate in our clinical trials because of negative publicity from adverse events in our clinical trials or in the biotechnology or protein therapeutics industries or for other reasons, including competitive clinical trials for similar patient populations, the timeline for recruiting patients, conducting studies and obtaining regulatory approval of potential products may be delayed. These delays could result in increased costs, delays in advancing our product development or termination of our clinical trials altogether. If we have difficulty enrolling and maintaining a sufficient number of patients to conduct our clinical

trials as planned for any reason, we may need to delay, limit or terminate clinical trials, any of which would have an adverse effect on our business, prospects, financial condition and results of operations.

Furthermore, clinical trial delays could also shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which could impair our ability to obtain orphan exclusivity and successfully commercialize our product candidates and may have an adverse effect on our business, financial condition and results of operations.

Our current product candidates and any other product candidates that we may develop from our discovery engine represent novel therapeutic approaches, which may cause significant delays or may not result in any commercially viable drugs.

We have concentrated the bulk of our research and development efforts to date on studying extracellular functions of tRNA synthetase biology, a newly discovered area of biology. We have also identified NRP2 as a receptor for efzofitimod and have focused research efforts on NRP2 biology. Our future success is highly dependent on the successful development of product candidates based on these new areas of biology, including efzofitimod, ATYR2810 and additional product candidates arising from proteins derived from tRNA synthetases or targeting the NRP2 receptor or other pathways, including Alanyl-tRNA synthetase (AARS) and Aspartyl-tRNA synthetase (DARS). Extracellular tRNA synthetase-based biology and NRP2 biology represents a novel approach to drug discovery and development, and to our knowledge, no drugs have been developed using, or based upon, this approach. Despite the successful development of other naturally occurring proteins, such as erythropoietin and insulin, as therapeutics, proteins derived from HARS, AARS or DARS families or targeting the NRP2 receptor and from other tRNA synthetase pathways represent a novel class of protein therapeutics, and our development of these therapeutics is based on our new understanding of human physiology. In particular, the mechanism of action of tRNA synthetases and their role in immunomodulation and tissue regeneration have not been studied extensively, nor has the safety of this class of protein therapeutics been evaluated extensively in humans. The therapeutic product candidates that we elect to develop may not have the physiological functions that we currently ascribe to them, may have limited or no therapeutic applications, or may present safety problems of which we are not yet aware. We cannot be sure that our discovery engine will yield therapeutic product candidates that are safe, effective, approvable by regulatory authorities, manufacturable, scalable, or profitable.

Because our work represents a new therapeutic approach, developing and commercializing our product candidates, including efzofitimod and ATYR2810, subjects us to a number of challenges, including:

- defining indications within our targeted diseases and clinical endpoints within each indication that are appropriate to support regulatory approval, including with respect to our planned registrational study of efzofitimod and prioritization of outcome measurements that would best support the evaluation of efzofitimod's efficacy;
- obtaining regulatory approval from the FDA and other regulatory authorities that have little or no experience with the development of extracellular tRNA synthetase-based therapeutics;
- educating medical personnel regarding the potential side effect profile of each of our product candidates, such as the potential for the development of antibodies against our purified protein therapeutics;
- developing processes for the safe administration of these product candidates, including long-term follow-up for all patients who receive our product candidates;
- sourcing clinical and, if approved, commercial supplies for the materials used to manufacture and process our product candidates;
- developing a manufacturing process and distribution network that ensures consistent manufacture of our product candidates in compliance with current good manufacturing practices (cGMPs) and related requirements, with a cost of goods that allows for an attractive return on investment;
- obtaining and maintaining third-party coverage and adequate reimbursement of our product candidates;
- establishing sales and marketing capabilities after obtaining any regulatory approval to gain market acceptance; and
- developing therapeutics for diseases or indications beyond those addressed by our current product candidates.

Moreover, public perception of safety issues, including adoption of new therapeutics or novel approaches to treatment, may adversely influence the willingness of subjects to participate in clinical trials, or if approved, of physicians to adopt and prescribe novel therapeutics. Physicians, hospitals and third-party payors often are slow to adopt new products, technologies and treatment practices. Physicians may decide the therapy is too complex or unproven to adopt and may choose not to administer the therapy. Based on these and other factors, healthcare providers and payors may decide that the benefits of any therapeutic candidates for which we receive regulatory approval do not or will not outweigh its costs. Any inability to successfully develop commercially viable drugs would have an adverse impact on our business, prospects, financial condition and results of operations.

Data generated in our preclinical studies and patient sample data relating to the immunomodulatory domain of HARS, including efzofitimod, may not be predictive or indicative of the immunomodulatory activity or therapeutic effects, if any, of our product candidates in patients.

Our scientists discovered the activity of the immunomodulatory domain of HARS, including efzofitimod, using *in vitro* and *in vivo* screening systems designed to test potential immunomodulatory activity in animal models of immune activity or inflammation. Translational medicine, or the application of basic scientific findings to develop therapeutics that promote human health, is subject to a number of inherent risks. In particular, scientific hypotheses formed from preclinical observations may prove to be incorrect, and the data generated in animal models or observed in limited patient populations may be of limited value, and may not be applicable in clinical trials conducted under the controlled conditions required by applicable regulatory requirements and our protocols. For example, we have not extensively studied the activity of efzofitimod in patients with ILD.

Our classification of diseases based on the existence of excessive immune cell activation or lack thereof and our hypothesis that these represent potential indications for our product candidates may not prove to be therapeutically relevant. Accordingly, the conclusions that we have drawn from animal studies and patient sample data regarding the potential immunomodulatory activity of efzofitimod may not be substantiated in other animal models or in clinical trials. Further, based on the discovery of the involvement of NRP2 in the mechanism of action of efzofitimod, we are still expanding our knowledge of the role of the NRP2 pathway in regulating immune responses. Although we were able to establish clinical proof-of-concept for efzofitimod in our Phase 1b/2a clinical trial in patients with pulmonary sarcoidosis, this may not be validated in other clinical trials. Any failure to demonstrate in controlled clinical trials the requisite safety and efficacy of our product candidates will adversely affect our business, prospects, financial condition and results of operations.

We have previously conducted and we or our third party collaborators may conduct additional clinical trials of efzofitimod outside of the United States. The FDA, however, may not accept data from such trials, in which case our development plans will be delayed, which could materially harm our business.

In June 2018, we completed a Phase 1 clinical trial of efzofitimod in healthy subjects in Australia. This randomized, double-blind, placebo-controlled study investigated the safety, tolerability, immunogenicity, and PK of intravenous efzofitimod in 36 healthy volunteers. In addition, we or our third party collaborators may choose to conduct additional clinical trials for efzofitimod in countries outside the United States, subject to applicable regulatory approval. For example, our partner, Kyorin Pharmaceutical Co., Ltd. (Kyorin), conducted an efzofitimod Phase 1 clinical trial in healthy volunteers in Japan.

Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of such study data is generally subject to certain conditions. For example, in cases where data from foreign clinical trials are intended to serve as the basis for marketing approval in the United States, the FDA will generally not approve the application on the basis of foreign data alone unless (i) the data are applicable in the U.S. population and U.S. medical practice; and (ii) the trials were performed by clinical investigators of recognized competence and pursuant to GCP regulations. Additionally, the FDA's clinical trial requirements, including sufficient size of patient populations and statistical powering, must be met. In addition, when studies are conducted only at sites outside of the United States, the FDA generally does not provide advance comment on the clinical protocols for the studies, and therefore there is an additional risk that the FDA could determine that the study design or protocol for a non-U.S. clinical trial was inadequate, which would likely require us to conduct additional clinical trials, in which case our development plans will be delayed, which could materially harm our business.

Conducting clinical trials outside the United States also exposes us to additional risks, including risks associated with:

- additional foreign regulatory requirements;
- foreign exchange fluctuations;
- compliance with foreign manufacturing, customs, shipment and storage requirements;
- cultural differences in medical practice and clinical research; and
- diminished protection of intellectual property in some countries.

Further, as a result of the ongoing COVID-19 pandemic, the integrity of data from any clinical trials conducted outside of the United States may not be acceptable to the FDA.

Our therapeutic product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following marketing approval, if any.

Undesirable side effects caused by our product candidates, or safety, tolerability or toxicity issues that may occur in our preclinical studies, clinical trials or in the future, could cause us or regulatory authorities to interrupt, restrict, 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 other comparable foreign authorities.

In our Phase 1b/2 clinical trials for our first clinical trial candidate, ATYR1940 (slightly truncated recombinant HARS protein), completed in 2016 and 2017, we observed low levels of antibodies to ATYR1940 in some subjects in response to the administration of ATYR1940. Although these antibody observations were without associated clinical symptoms, the development of higher levels of such antibodies over a longer course of treatment may ultimately limit efficacy and trigger a negative autoimmune response. In addition, some patients in our Phase 1b/2 clinical trials of ATYR1940 experienced generalized infusion related reactions (IRRs) and discontinued dosing. We established procedural measures, including a decreased concentration and intravenous delivery rate of ATYR1940, in an effort to minimize the occurrence of generalized IRRs and the formation of anti-drug antibodies. After implementation of these procedures, we observed a decreased rate of IRRs in our clinical trials of ATYR1940. We did not observe IRRs in our Phase 1b/2a clinical trial of efzofitimod in patients in pulmonary sarcoidosis or in our other efzofitimod clinical trials, but we cannot assure that this will be the case in any future clinical trials. Generalized IRRs and other complications or side effects could harm further development and/or commercialization of our product candidates, including efzofitimod. Additionally, our product candidates are designed to be administered by intravenous injection, which may cause side effects, including acute immune responses and injection site reactions. The risk of adverse immune responses remains a significant concern for protein therapeutics, and we cannot assure that these or other risks will not occur in any of our clinical trials our product candidates. There is also a risk of delayed adverse events as a result of long-term exposure to protein therapeutics that must be administered repeatedly for the management of chronic conditions, such as the development of antibodies, which may occur over time. If any such adverse events occur, which may include the development of a negative autoimmune response from antibodies or the occurrence of IRRs associated with antibodies, further advancement of our clinical trials could be halted or delayed, which would have a material adverse effect on our business, prospects, financial condition and results of operations.

If one or more of our product candidates receives marketing approval, and we or others later identify undesirable side effects or other safety concerns caused by such products, a number of potentially significant negative consequences could result.

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

We may not be successful in our efforts to identify or discover additional product candidates.

A key element of our strategy is to expand applications of efzofitimod to additional immune-mediated diseases, advance the development of ATYR2810 for cancer indications and leverage our discovery engine to identify the therapeutic potential of NRP2 biology and extracellular proteins derived from tRNA synthetases to help identify or discover additional product candidates. A significant portion of the research that we are conducting involves new compounds and drug discovery methods, including our proprietary technology. Our drug discovery activities using our proprietary technology may not be successful in identifying product candidates that are useful in treating diseases. Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for a number of reasons, including:

- the research methodology used may not be successful in identifying appropriate potential product candidates; or
- potential product candidates may, on further study, be shown to have harmful side effects or other characteristics that indicate that they are unlikely to be product candidates that will receive marketing approval and achieve market acceptance.

Research programs to identify new product candidates require substantial technical, financial and human resources. We may choose to focus our efforts and resources on a potential product candidate that ultimately proves to be unsuccessful. If we are unable to identify suitable product candidates for preclinical and clinical development and regulatory approval, we will not be able to generate product revenues, which would have an adverse impact on our business, prospects, financial condition and results of operations.

We may face manufacturing stoppages and other challenges associated with the clinical or commercial manufacture of our product candidates.

All entities involved in the preparation of therapeutics for clinical trials or commercial sale, including our existing CDMOs for our product candidates, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or use in late-stage clinical trials must be manufactured in accordance with cGMP. These regulations govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of contaminants or to inadvertent changes in the properties or stability of our product candidates that may not be detectable in final product testing. We or our CDMOs must supply all necessary documentation in support of a biological license

application (BLA) on a timely basis and must adhere to the FDA's Good Laboratory Practices and cGMP regulations enforced by the FDA through its facilities inspection program. The facilities and quality systems of our CDMOs and other CROs must pass a pre-approval inspection for compliance with applicable regulations as a condition of regulatory approval of our product candidates. If these facilities do not pass a pre-approval plant inspection, FDA approval of the products will not be granted. If global health concerns prevent the FDA or other regulatory authorities from conducting their regular inspections, it could impact the ability of our CDMOs to provide us with product for clinical trials.

The regulatory authorities also may, at any time following approval of a product for sale, audit the facilities in which the product is manufactured. If any such inspection or audit of our facilities or those of our CDMOs and CROs identifies a failure to comply with applicable regulations or if a violation of our product specifications or applicable regulations occurs independently of such an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly or time-consuming for us or a third party to implement and that may include the temporary or permanent suspension of a clinical trial or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business.

In addition, quarantines, shelter-in-place and similar government orders, or the perception that such orders, shutdowns or other restrictions on the conduct of business operations could occur, related to the ongoing COVID-19 pandemic or other infectious diseases could impact personnel at our CDMOs and CROs, which could disrupt our clinical timelines and have a material adverse impact on our business, prospects, financial condition and results of operations. Additionally, the production of COVID-19 vaccines may disrupt the availability of raw materials and consumables required to manufacture our product candidates, which could result in decreased manufacturing and supply of these product candidates to support our planned clinical trials or regulatory filings.

If we or any of our CDMOs and CROs fail to maintain regulatory compliance, the FDA can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new biologic product, or revocation of a pre-existing approval. Additionally, if supply from one approved manufacturer is interrupted, there could be a significant disruption in clinical or commercial supply. An alternative manufacturer would need to be qualified through a BLA supplement which could result in further delay. The regulatory agencies may also require additional studies if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

In addition, the manufacture of our product candidates presents challenges associated with biologics production, including the inherent instability of larger, more complex molecules and the need to ensure uniformity of the drug substance produced in different facilities or across different batches. The process of manufacturing biologics is extremely susceptible to product loss due to contamination, equipment failure or improper installation or operation of equipment, or vendor or operator error. Even minor deviations from normal manufacturing and distribution processes for any of our product candidates could result in reduced production yields, product defects, and other supply disruptions. Furthermore, although tRNA synthetases represent a class of proteins that may share immunomodulatory properties in various physiological pathways, each tRNA synthetase has a different structure and may have unique manufacturing requirements that are not applicable across the entire class. For example, fusion proteins, such as efzofitimod, include an additional antibody domain to improve PK characteristics, and may therefore require a more complex and time-consuming manufacturing process than other tRNA synthetase-based therapeutic candidates. Currently, we are producing our efzofitimod molecule in *E.coli* by expression in inclusion bodies and refolding to recreate the native structure. The manufacturing processes for one of our product candidates may not be readily adaptable to other product candidates that we develop, and we may need to engage multiple third-party manufacturers to produce our product candidates. For example, we recently engaged an additional CDMO to manufacture efzofitimod and will need to complete a technology transfer and validation process before the new CDMO will be able to produce additional bulk drug substance for our clinical trials or otherwise. Any adverse developments affecting manufacturing operations for our product candidates may result in shipment delays, inventory shortages, lot failures, withdrawals or recalls or other interruptions in the supply of our drug substance and drug product which could delay the development of our product candidates. We may also have to write off inventory, incur other charges and expenses for supply of drug product that fails to meet specifications or expires, undertake costly remediation efforts, or seek more costly manufacturing alternatives. Any manufacturing stoppage or delay, or any inability to consistently manufacture adequate supplies of our product candidates for our clinical trials or on a commercial scale will harm our business, prospects, financial condition and results of operations.

Even if we complete the necessary preclinical studies and clinical trials, we cannot predict when or if we will obtain regulatory approval to commercialize a product candidate, and the scope of any approval may be narrower than we expect.

We cannot commercialize a product until the appropriate regulatory authorities have reviewed and approved the product candidate. Even if our product candidates demonstrate safety and efficacy in clinical trials, the regulatory agencies may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval.

Additional delays may result if an FDA advisory committee or regulatory authority recommends non-approval or restrictions on approval. In addition, we may experience delays or rejections based upon additional government regulation from future legislation

or administrative action, or changes in regulatory agency policy during the period of product development, clinical trials and the review process. Regulatory agencies also may approve a product candidate for fewer or more limited indications than requested, may impose restrictions on dosing or may grant approval subject to the performance of post-marketing studies. In addition, regulatory agencies may not approve the labeling claims that are necessary or desirable for the successful commercialization of our product candidates.

Although the FDA has recently granted orphan drug designation to efzofitimod for the treatment of sarcoidosis, we may not receive orphan drug designation for efzofitimod in other jurisdictions or for other indications that we may pursue, or for any other product candidates we may develop under any new applications for orphan drug designation that we may submit, and any orphan drug designations that we have received or may receive may not confer marketing exclusivity or other expected commercial benefits.

The FDA granted orphan drug designation to efzofitimod for the treatment of sarcoidosis. We may apply for orphan drug designation for efzofitimod for other indications and product candidates in the United States. Orphan drug status confers up to ten years of marketing exclusivity in Europe, and up to seven years of marketing exclusivity in the United States, for a particular product in a specified indication. Obtaining an orphan drug designation can be difficult and we cannot assure you that we will be able to obtain orphan drug designation in other jurisdictions or for other indications, or rely on orphan drug or similar designations to exclude other companies from manufacturing or selling products using the same principal mechanisms of action for the same indications that we pursue beyond these timeframes. Furthermore, marketing exclusivity in Europe can be reduced from ten years to six years if the initial designation criteria have significantly changed since the market authorization of the orphan product. Even if we are the first to obtain marketing authorization for an orphan drug indication, there are circumstances under which a competing product may be approved for the same indication during the period of marketing exclusivity, such as if the later product is shown to be clinically superior to the orphan product, or if the later product is deemed a different product than ours. Further, the marketing exclusivity would not prevent competitors from obtaining approval of the same product candidate as ours for indications other than those in which we have been granted orphan drug designation, or for the use of other types of products in the same indications as our orphan product.

A breakthrough therapy or fast track designation by the FDA may not lead to expedited development or regulatory review or approval.

We may seek, from time to time, breakthrough therapy or fast track designation for our product candidates. A breakthrough therapy designation is for a product candidate intended to treat a serious or life-threatening condition, and preliminary clinical evidence indicates that the product candidate may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies. A fast track designation is for a product candidate that treats a serious or life-threatening condition, and preclinical or clinical data demonstrate the potential to address an unmet medical need. The FDA has broad discretion whether or not to grant these designations. Accordingly, even if we believe a particular product candidate is eligible for breakthrough therapy or fast track designation, we cannot assure you that the FDA would decide to grant it. Even if we receive breakthrough therapy or fast track designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw breakthrough therapy or fast track designation if it believes that the product no longer meets the qualifying criteria. In addition, the breakthrough therapy program is a relatively new program. As a result, we cannot be certain whether any of our product candidates can or will qualify for breakthrough therapy designation. Our business may be harmed if we are unable to avail ourselves of these or any other expedited development and regulatory pathways.

Disruptions at the FDA and other government agencies caused by funding shortages or global health concerns could negatively impact our business.

The ability of the FDA to review and approve proposed clinical trials or new products can be affected by a variety of factors, including government budget and funding levels, statutory, regulatory, and policy changes, the FDA's ability to hire and retain key personnel and accept the payment of user fees, and other events that may otherwise affect the FDA's ability to perform routine functions. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of other government agencies 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 product candidates to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including for 35 days beginning on December 22, 2018, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical FDA employees and stop critical activities.

Even if we obtain regulatory approval for a product candidate, our products will remain subject to regulatory scrutiny.

Even if we obtain regulatory approval for a product candidate, such product will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping, conduct of post-marketing studies, adverse event reporting and submission of safety, efficacy, and other post-market information, including both federal and state requirements in the United States and requirements of comparable foreign regulatory authorities.

We and our CDMOs will be subject to continual review and inspections to assess compliance with cGMP and adherence to commitments made in any BLA or marketing authorization application (MAA). Accordingly, we and others with whom we work will need to continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production, and quality control.

Any regulatory approvals that we receive for our product candidates may be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials, and surveillance to monitor the safety and efficacy of the product candidate. If new safety issues emerge, we may be required to change our labeling. Any new legislation addressing drug safety or efficacy issues could result in delays in product development or commercialization, or increased costs to assure compliance.

We will have to comply with requirements concerning advertising and promotion for our products. Violations, including actual or alleged promotion of our products for unapproved, or off-label, uses are subject to enforcement letters, inquiries and investigations, and civil and criminal sanctions. Any actual or alleged failure to comply with labeling and promotion requirements may have a negative impact on our business. In the United States, engaging in impermissible promotion of our products for off-label uses can also subject us to false claims litigation under federal and state statutes, which can lead to civil and criminal penalties and fines, agreements that would materially restrict the manner in which we promote or distribute our drug products and exclusion from Medicare, Medicaid and other federal and state healthcare programs. These false claims statutes include the federal False Claims Act, which allows any individual to bring a lawsuit against a pharmaceutical company on behalf of the federal government alleging submission of false or fraudulent claims, or causing to present such false or fraudulent claims, for payment by a federal program such as Medicare or Medicaid. If the government prevails in the lawsuit, the individual will share in any fines or settlement funds. If we do not lawfully promote our approved products, we may become subject to such litigation and, if we are not successful in defending against such actions, those actions could compromise our ability to become profitable.

The holder of an approved BLA or MAA must submit new or supplemental applications and obtain approval for certain changes to the approved product, product labeling, or manufacturing process. We could also be asked to conduct post-marketing clinical trials to verify the safety and efficacy of our products in general or in specific patient subsets. If original marketing approval were obtained through an accelerated approval pathway, we could be required to conduct a successful post-marketing clinical trial to confirm clinical benefit for our products. An unsuccessful post-marketing study or failure to complete such a trial could result in the withdrawal of marketing approval.

If a regulatory agency discovers previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, or disagrees with the promotion, marketing or labeling of a product, such regulatory agency may impose restrictions on that product or us, including requiring withdrawal of the product from the market. If we fail to comply with applicable regulatory requirements, a regulatory agency or enforcement authority may, among other things:

- issue untitled or warning letters;
- impose civil or criminal penalties;
- suspend or withdraw regulatory approval;
- suspend any of our ongoing clinical trials;
- refuse to approve pending applications or supplements to approved applications submitted by us;
- impose restrictions on our operations, including closing our CDMOs' facilities; or
- seize or detain products, or require or request a product recall.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response, and could generate negative publicity. Any failure to comply with ongoing regulatory requirements may significantly and adversely affect our ability to commercialize and generate revenue from our products. If regulatory sanctions are applied or if regulatory approval is withdrawn, the value of our company and our operating results will be adversely affected.

Risks related to our reliance on third parties

We depend on our existing collaborations and may depend on collaborations with additional third parties for the development and commercialization of certain of our product candidates. If our collaborations are not successful, we may not be able to capitalize on the market potential of these product candidates.

We have entered into, and may continue to enter into, research collaborations for the research and development of specified product candidates. Our sole source of revenue depends upon the performance by these collaborators of their responsibilities under

these arrangements. For example, while we are eligible to receive up to an additional $165.0 million in milestone payments under the Kyorin Agreement, as well as tiered royalties ranging from the mid-single digits to mid-teens on net sales in Japan, whether and when we receive these payments will depend on Kyorin's development and commercialization of efzofitimod in Japan, over which we have limited control. The development efforts of our collaborators are subject to the same risks and uncertainties described above with respect to our independently developed product candidates.

Some collaborators may not succeed in their product development efforts. It is possible that our collaborators may be unable to obtain regulatory approval of our product candidates or successfully market and commercialize any such products for which regulatory approval is obtained. For example, while we received a $2.0 million milestone payment in January 2021, if Kyorin's operations are limited due to the impacts of the ongoing COVID-19 pandemic in Japan or in other regions where Kyorin operates or relies on third party operations, the development of efzofitimod in Japan may be significantly delayed and adversely affected, which may in turn delay or limit our receipt of any additional payments under the Kyorin Agreement. Other collaborators may not devote sufficient time or resources to the programs covered by these arrangements, and we may have limited or no control over the time or resources allocated by these collaborators to these programs. The occurrence of any of these events may cause us to derive little or no revenue from these arrangements, lose opportunities to validate our product candidates, or force us to curtail or cease our development efforts in these areas.

Our collaborators may breach or terminate their agreements with us, including termination without cause at subject to certain prior written notice requirements, and we may be unsuccessful in entering into and maintaining other collaborative arrangements for the development of product candidates. For example, Kyorin has the right to terminate the agreement for any reason upon 90 days advance written notice to us. In addition, if we are unable to maintain existing collaboration arrangements or enter into new ones, our ability to generate licensing, milestone or royalty revenues would be materially impaired.

We rely, and expect to continue to rely, on third parties to conduct some or all aspects of our product manufacturing, protocol development, research and preclinical and clinical testing, and these third parties may not perform satisfactorily.

We currently rely, and expect to continue to rely, on third parties to conduct some or all aspects of product manufacturing, protocol development, research and preclinical and clinical testing with respect to our product candidates. Any of these third parties may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it could delay our product development activities. Our reliance on these third parties for research and development activities reduces our control over these activities but does not relieve us of our responsibility to ensure compliance with all required regulations and study protocols. For example, for any product candidates that we develop and commercialize on our own, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable study plan and protocols and GCPs so long as we continue to develop and commercialize on our own.

If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our research and development activities, including clinical trials, in accordance with regulatory requirements or our stated study plans and protocols, we will not be able to complete, or may be delayed in completing, the preclinical studies and clinical trials required to support future BLA submissions and approval of our product candidates.

We rely and intend to rely on third parties to produce preclinical, clinical and commercial supplies of our product candidates.

Other than some internal capacity to support preclinical activities, we do not have, nor do we plan to acquire, the infrastructure or capability internally to manufacture our preclinical and clinical quantities of our product candidates, and we lack the internal resources and capability to manufacture any of our product candidates on a clinical or commercial scale. Reliance on CDMOs and CROs entails risks to which we would not be subject if we manufactured the product candidates ourselves, including:

- the inability to negotiate manufacturing agreements with third parties under commercially reasonable terms;
- reduced control as a result of using third-party CDMOs and CROs for all aspects of manufacturing activities;
- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us; and
- disruptions to the operations of our CDMOs, CROs or suppliers caused by conditions unrelated to our business or operations, including the insolvency or bankruptcy of the CDMOs, CROs or supplier.

Any of these events could lead to clinical trial delays or failure to obtain regulatory approval, or impact our ability to successfully commercialize future products. Some of these events could be the basis for FDA action, including injunction, recall, seizure or total or partial suspension of production.

Additionally, each CDMO may require licenses to manufacture our product candidates or components thereof if the applicable manufacturing processes are not owned by the CDMO or in the public domain, and we may be unable to transfer or sublicense the intellectual property rights we may have with respect to such activities. These factors could cause the delay of clinical development, regulatory submissions, required approvals or commercialization of our product candidates, cause us to incur higher costs and prevent us from commercializing our products successfully.

We currently rely on a single CDMO for process development and scale-up of efzofitimod, including the manufacture of bulk drug substance for our projected needs for initial clinical trials. We have recently entered an agreement with another CDMO for the transfer of the process, scale-up and manufacturing of bulk drug substance for future clinical trials. Subject to the satisfactory completion of process validation and other requirements, we may contract with this CDMO for larger scale commercial manufacturing. We rely on a single CDMO for process development and scale-up of ATYR2810. We do not have long-term contracts with our CDMOs, and our CDMOs may terminate their agreements with us for a variety of reasons including technical issues or our material breach of our obligations under the applicable agreement. Furthermore, our CDMOs may reallocate resources away from the production of our product candidates if we delay manufacturing under certain circumstances, and the manufacturing facilities in which our product candidates are made could be adversely affected by earthquakes and other natural disasters, labor shortages, power failures, and numerous other factors. If our CDMOs fail to meet contractual requirements, and we are unable to secure one or more replacement CDMOs capable of production at a substantially equivalent cost, our clinical development activities may be delayed, or we could lose potential revenue. Manufacturing biologic drugs is complicated and tightly regulated by the FDA and comparable regulatory authorities around the world, and although alternative CDMOs with the necessary manufacturing and regulatory expertise and facilities exist, it could be expensive and take a significant amount of time to arrange for alternative CDMOs, transfer manufacturing procedures to these alternative CDMOs, and demonstrate comparability of material produced by such new CDMOs. New CDMOs of any product would be required to comply with applicable regulatory requirements. These CDMOs may not be able to manufacture our product candidates at costs, or in quantities, or in a timely manner necessary to complete the clinical development of our product candidates or make commercially successful products.

We rely, and expect to continue to rely, on third parties to conduct, supervise and monitor our clinical trials, and if these third parties perform in an unsatisfactory manner, it may harm our business.

We have relied, and expect to continue to rely, on third-party CROs, clinical investigators and clinical trial sites to ensure our clinical trials are conducted properly and on time. While we have and will continue to enter into agreements governing their activities, we will have limited influence over their actual performance. We will control only certain aspects of our CROs' activities. Nevertheless, we will be responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, legal and regulatory requirements, and scientific standards, and our reliance on the CROs does not relieve us of our regulatory responsibilities.

We and our investigators and CROs are required to comply with GCPs for conducting, recording and reporting the results of clinical trials to assure that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical trial participants are protected. The FDA enforces GCPs through periodic inspections of study sponsors, principal investigators and clinical trial sites. If we or our investigators and CROs fail to comply with applicable GCPs, the clinical data generated in our future clinical trials may be deemed unreliable and the FDA may require us to perform additional unanticipated clinical trials before approving any marketing applications. Upon inspection, the FDA may determine that our clinical trials did not comply with GCPs. In addition, our future clinical trials will require a sufficient number of test subjects to evaluate the safety and effectiveness of our product candidates. Accordingly, if our investigators and CROs fail to comply with these regulations or fail to recruit a sufficient number of patients, we may be required to repeat such clinical trials, which would delay the regulatory approval process.

Our investigators and CROs are not our employees, and we are therefore unable to directly monitor whether or not they devote sufficient time and resources to our clinical and preclinical programs. They may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other drug development activities that could harm our competitive position. If our investigators or CROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, 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 any other reasons, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for, or successfully commercialize our product candidates. As a result, our financial results would be harmed, our costs could increase, our ability to generate revenues could be delayed and the commercial prospects for our product candidates will be adversely affected.

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.

We rely on third parties to manufacture our product candidates, and we collaborate with both industry and various academic institutions in the development of our discovery engine for therapeutic applications based on tRNA synthetase biology. In connection with these activities, we are required, at times, to 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 the contractual provisions employed when working with third parties, the need to share 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 have a material adverse effect on our business, prospects, financial condition and results of operations.

In addition, these agreements typically restrict the ability of our collaborators, advisors, employees and consultants to publish data potentially relating to our trade secrets. Our academic collaborators typically have rights to publish data, provided that we are notified in advance and may delay publication for a specified time in order to secure intellectual property rights to which we are entitled arising from the collaboration. In other cases, publication rights are controlled exclusively by us, although in some cases we may share these rights with other parties. We also conduct joint research and development programs that may require us to share trade secrets under the terms of our research and development partnerships or similar agreements. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of these agreements, independent development or publication of information including our trade secrets in cases where we do not have proprietary or otherwise protected rights at the time of publication. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business, prospects, financial condition and results of operations.

Risks related to our intellectual property

If we are unable to obtain, maintain or protect intellectual property rights related to our product candidates, or if the scope of such intellectual property protection is not sufficiently broad, we may not be able to compete effectively in our markets.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our technologies and product candidates. Our success depends in large part on our and our licensors' abilities to obtain and maintain patent and other intellectual property protection in the United States and in other countries for our proprietary technology and product candidates.

We have sought to protect our proprietary position by filing patent applications in the United States and abroad related to our novel technologies and product candidates that are important to our business. This process is expensive and time consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection.

The patentability of inventions, and the validity, enforceability and scope of patents in the biotechnology and pharmaceutical fields involves complex legal and scientific questions and can be uncertain. As a result, patent applications that we own or in-license may not issue as patents with claims that cover our product candidates, or at all, in the United States or in foreign countries for many reasons. For example, there is no assurance that we were the first to invent or the first to file patent applications in respect of the inventions claimed in our patent applications or that our patent applications claim patentable subject matter. We may also be unaware of potentially relevant prior art relating to our patents and patent applications, and this prior art, if any, may be used by third parties as grounds to seek to invalidate a patent or to prevent a patent from issuing from a pending patent application. Even if patents do successfully issue and even if such patents disclose aspects of our product candidates, third parties may challenge their validity, enforceability or scope, which may result in such patents being narrowed or invalidated. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property, provide exclusivity for our product candidates or prevent others from designing around our claims. If the breadth or strength of protection provided by the patents and patent applications we hold, license or pursue with respect to our product candidates is threatened, it could threaten our ability to commercialize our product candidates. Further, if we encounter delays in our clinical trials, the period of time during which we could market any of our product candidates under patent protection, if approved, would be reduced. Since patent applications in the United States and most other countries are confidential for a period of time after filing, we cannot be certain that we were the first to file any patent application related to our product candidates. Changes to the patent laws in the United States and other jurisdictions could also diminish the value of our patents and patent applications or narrow the scope of our patent protection. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

If the patent applications we own or have in-licensed that relate to our programs or product candidates do not issue as patents, if their breadth or strength of protection is threatened, or if they fail to provide exclusivity for our product candidates, it could dissuade companies from collaborating with us to develop product candidates, and threaten our ability to commercialize future products. We cannot offer any assurances about which, if any, patents will issue, the breadth of any such patents or whether any issued patents will be found invalid and unenforceable or will be threatened by third parties. Any successful opposition to these patents or any other

patents owned by or licensed to us could deprive us of rights necessary for the successful commercialization of any product candidates that we may develop. In addition, patents have a limited term. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Although various extensions may be available, the life of a patent, and the protection it affords, is limited. Even if a patent does issue for any of our pending patent applications, possible delays in regulatory approvals could mean that the period of time during which we could market a product candidate under patent protection could be reduced from what we generally would expect. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we were the first to file any patent application related to a product candidate. Furthermore, if third parties have filed such patent applications, an interference proceeding in the United States can be initiated by a third party to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. Even if patents covering aspects of our product candidates are obtained, once the patent life has expired for a product, we may be open to competition from generic medications.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and contractors. 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, but it is possible that these security measures could be breached. Although we expect all of our employees and consultants to assign their inventions to us, and all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. For example, 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. Misappropriation or unauthorized disclosure of our trade secrets could impair our competitive position and may have a material adverse effect on our business. Additionally, if the steps we take to maintain the confidentiality of our trade secrets are inadequate, we may have insufficient recourse against third parties for misappropriating our proprietary information and processes. In addition, others may independently discover our trade secrets and proprietary information. For example, the FDA, as part of its Transparency Initiative, is currently considering whether to make additional information publicly available on a routine basis, including information that we may consider to be trade secrets or other proprietary information, and it is not clear at the present time how the FDA's disclosure policies may change in the future, if at all.

If due to the ongoing COVID-19 pandemic we are unable to generate new animal, or *in vitro* data, in time to support new, or updated patent application filings, or prior to patent conversion deadlines, it could materially impact the enforceability or scope of those patent filings.

If we are unable to prevent material disclosure of the non-patented intellectual property related to our technologies to third parties, and there is no guarantee that we will have any such enforceable trade secret protection, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition.

Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in preventing third parties from practicing our inventions in countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions.

Claims that our product candidates or the manufacture, sale or use of our future products infringe the patent or other intellectual property rights of third parties could result in costly litigation or could require substantial time and money to resolve, even if litigation is avoided.

Our commercial success depends in part on our avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions and inter partes reexamination proceedings before the United States Patent and Trademark Office (USPTO) and corresponding foreign patent offices. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are pursuing development candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the

use or manufacture of our product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our product candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our product candidates, any molecules formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block our ability to commercialize such product candidate unless we obtained a license under the applicable patents, or until such patents expire.

Similarly, if any third-party patents are held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or methods of use, the holders of any such patents may be able to block our ability to develop and commercialize the applicable product candidate unless we obtain a license or until such patent expires. In either case, such a license may not be available on commercially reasonable terms or at all.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our product candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products or obtain one or more licenses from third parties, which may not be able to be obtained on reasonable commercial terms or at all, or require substantial time and monetary expenditure.

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

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

We may not be successful in obtaining or maintaining necessary rights to our therapeutic product candidates and processes for our development pipeline through acquisitions and in-licenses.

We believe that we have rights to intellectual property, through licenses from third parties and under patents that we own, that is necessary or useful to develop our product candidates. Because our programs may involve additional product candidates that may require the use of proprietary rights held by third parties, the growth of our business will likely depend in part on our ability to acquire, in-license or use these proprietary rights. In addition, our product candidates may require specific formulations to work effectively and efficiently and these rights may be held by others. We may be unable to acquire or in-license any compositions, methods of use, processes or other third-party intellectual property rights from third parties that we identify on reasonable commercial terms or at all. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies are also 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, cash resources and greater clinical development and commercialization capabilities.

We sometimes collaborate with U.S. and foreign academic institutions to accelerate our preclinical research or development under written agreements with these institutions. These institutions may provide us with an option to negotiate a license to the institution's rights in technology resulting from the collaboration. Regardless of any such right of first negotiation for intellectual property, we may be unable to negotiate a license within the specified time frame or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program.

In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment. If we are unable to successfully obtain rights to required third-party intellectual property rights, our business, financial condition and prospects for growth could suffer.

If we fail to comply with our obligations in the agreements under which we license intellectual property rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business.

We are a party to a number of intellectual property license agreements that are important to our business and expect to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that future license agreements will impose, various diligence, milestone payment, royalty and other obligations on us. If we fail to comply with our obligations under

these agreements, or we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we would not be able to market products covered by the license.

We may need to obtain licenses from third parties to advance our research or allow commercialization of our product candidates, and we have done so from time to time. We may fail to obtain any of these licenses at a reasonable cost or on reasonable commercial terms, if at all. In that event, we may be required to expend significant time and resources to develop or license replacement technology. If we are unable to do so, we may be unable to develop or commercialize the affected product candidates, which could harm our business significantly. We cannot provide any assurances that third-party patents do not exist which might be enforced against our current product candidates or future products, resulting in either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties or other forms of compensation to third parties.

In some cases, patent prosecution of our licensed technology is controlled by the licensor. If our licensors fail to obtain and maintain patent or other protection for the proprietary intellectual property we license from them, we could lose our rights to the intellectual property or our exclusivity with respect to those rights, and our competitors could market competing products using such intellectual property. In certain cases, we may control the prosecution of patents resulting from licensed technology. In the event we breach any of our obligations related to such prosecution, we may incur significant liability to our licensors. Licensing of intellectual property is of critical importance to our business and involves complex legal, business and scientific issues and is complicated by the rapid pace of scientific discovery in our industry. Disputes may arise regarding intellectual property subject to a license agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the license agreement;
- the sublicensing of patent and other rights under our collaborative development relationships;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our sublicensees or partners, if any; and
- the priority of invention of patented technology.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates.

We may become involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time-consuming and unsuccessful.

Competitors may infringe or otherwise violate our patents, the patents of our licensors or our other intellectual property rights. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. Any claims that we assert against perceived infringers could also provoke these parties to assert counterclaims against us alleging that we infringe their intellectual property rights. In addition, in an infringement proceeding, a court may decide that a patent of ours or our licensors is not valid, is unenforceable or is not infringed, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing.

Interference or derivation proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions or other matters of inventorship with respect to our patents or patent applications or those of our licensors. We may also become involved in other proceedings, such as re-examination or opposition proceedings, before the USPTO or its foreign counterparts relating to our intellectual property or the intellectual property rights of others. An unfavorable outcome in any such proceedings could require us to cease using the related technology or to attempt to license rights to it from the prevailing party, or could cause us to lose valuable intellectual property rights. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms, if any license is offered at all. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States. In addition, the uncertainties associated with litigation could have a material adverse effect on our ability to raise the funds necessary to continue our clinical trials, continue our research programs, license necessary technology from third parties, or enter into development partnerships that would help us bring our product candidates to market. We may also become involved in disputes with others regarding the ownership of intellectual property rights. For example, we jointly develop intellectual property with certain parties, and disagreements may therefore arise as to the ownership of the intellectual

property developed pursuant to these relationships. If we are unable to resolve these disputes, we could lose valuable intellectual property rights.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties or that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

We employ individuals who were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and independent contractors 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 our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed intellectual property, including trade secrets or other proprietary information, of any of our employee's former employer or other third parties. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could adversely impact our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

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

We may be subject to claims that former employees, collaborators or other third parties have an ownership interest in our patents or other intellectual property. For example, we may have inventorship disputes arise from conflicting obligations of consultants or others who are involved in developing our product candidates. Litigation may be necessary to defend against these and other claims challenging inventorship or ownership, or we may enter into agreements to clarify the scope of our rights in such intellectual property. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

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

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents or applications will be due to be paid to the USPTO and various governmental patent agencies outside of the United States in several stages over the lifetime of the patents or applications. We have systems in place to remind us to pay these fees, and we employ an outside firm and rely on our outside counsel to pay these fees due to non-U.S. patent agencies. The USPTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. We employ law firms and other professionals to help us comply, and in many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, there are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, our competitors might be able to enter the market and this circumstance would have a material adverse effect on our business.

Issued patents covering our product candidates could be found invalid or unenforceable if challenged in court.

If we or one of our licensors initiated legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that the patent covering our product candidate is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. Third parties may also raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review, and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). Such proceedings could result in revocation or amendment to our patents in such a way that they no longer cover our product candidates. 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 our product candidates. Such a loss of patent protection would have a material adverse impact on our business.

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

As is the case with many other biotechnology companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology industry involve both technological and legal complexity, and therefore obtaining, maintaining and enforcing biotechnology patents is costly, time-consuming and inherently uncertain. In addition, recent legislative and judicial developments in the United States and elsewhere have in some cases removed the protection afforded to patent owners, made patents more difficult to obtain, or increased the uncertainty regarding the ability to obtain, maintain and enforce patents. For example, Congress has recently passed, and the United States is currently implementing, wide-ranging patent reform legislation, and may pass further patent reform legislation in the future. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. For example, in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, the U.S. Supreme Court held that certain claims to naturally occurring substances are not patentable. Although we do not believe that any of the patents owned or licensed by us will be found invalid based on this decision, we cannot predict how future decisions by the courts, the U.S. Congress, or the USPTO may impact the value of our patents. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents generally, once obtained. Depending on decisions and actions by the U.S. Congress, the federal courts, the USPTO and their respective foreign counterparts, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to maintain and enforce our existing patents and patents that we might obtain in the future.

Patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the validity or defense of our issued patents.

On September 16, 2011, the Leahy-Smith America Invents Act (the Leahy-Smith Act) was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law, including provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. The USPTO is developing 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, and in particular, the first to file provisions, were enacted March 16, 2013. Although it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

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

Filing, prosecuting and defending patents on 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 to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent 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. 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.

Risks related to our business operations

We may use our financial and human resources to pursue a particular business strategy, research program or product candidate and fail to capitalize on strategies, programs or product candidates that may be more profitable or for which there is a greater likelihood of success.

Because we have limited resources, we may forego or delay pursuit of certain strategic opportunities or opportunities with certain programs, product candidates or indications that later prove to have greater commercial potential. We may focus on or pursue one indication over another potential indication and such development efforts may not be successful, which would cause us to delay the clinical development and approval of efzofitimod, ATYR2810 and other product candidates. In addition, our decisions as to which of our discovery programs to advance into preclinical and clinical development could preclude us from advancing others. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. In addition, we may elect to pursue a research, clinical or commercial strategy that ultimately does not yield the results that we desire. Our spending on current and future research and development programs for product candidates may not result in any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate, or we may allocate internal resources to a product candidate in a therapeutic area or market in which it would have been more advantageous to enter into a partnering arrangement. Any failure to allocate resources or capitalize on strategies in a successful manner will have an adverse impact on our business.

Our business could continue to be adversely affected by the effects of the ongoing COVID-19 pandemic.

Our business has been adversely affected by the effects of the ongoing COVID-19 pandemic and could continue to be adversely affected in the future. For example, many of our employees began telecommuting during the onset of the ongoing COVID-19 pandemic as states and municipalities announced aggressive actions to reduce the spread of the disease such as “shelter in place” orders, and some employees continue to do so, which has impacted certain of our operations and may continue to do so over the long term. We may experience further limitations on employee resources in the future, including because of sickness of employees or their families. The effects of government actions and our own policies and those of third parties to reduce the spread of COVID-19 have negatively impacted productivity and slowed down or delayed our ongoing and future clinical trials, preclinical studies and research and development activities, and may cause disruptions to our supply chain. In the event that government authorities were to again implement restrictions, including due to the emergence of new variants of COVID-19, our employees who currently are not telecommuting may no longer be able to access our facilities, and our operations may be further limited or curtailed.

During the ongoing COVID-19 pandemic, we may experience ongoing disruptions that could severely impact our business, preclinical studies and clinical trials, including:

- delays in receiving approval from local regulatory authorities to initiate future clinical trials;
- delays or difficulties in enrolling and retaining patients in our planned clinical trials;
- delays in clinical sites receiving the supplies and materials needed to conduct our clinical trials, including as a result of manufacturing delays and interruptions in global shipping that may affect the transport of clinical trial materials;
- changes in local regulations as part of a response to the ongoing 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;
- 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;
- interruption of key clinical trial activities, such as clinical trial site monitoring, due to limitations on travel imposed or recommended by federal or state governments, employers and others, or interruption of clinical trial subject visits and study procedures, the occurrence of which could affect the integrity of clinical trial data;
- interruption or delays in the operations of the FDA or other regulatory authorities, which may impact review and approval timelines;
- risk that participants enrolled in future clinical trials will contract COVID-19, or a variant thereof, while the clinical trial is ongoing, which could impact the results of the clinical trial, including by increasing the number of observed adverse events;
- risk that the production of COVID-19 vaccines may disrupt the availability of raw materials and consumables required to manufacture our product candidates, which could result in decreased manufacturing and supply of these product

candidates to support our planned clinical trials or regulatory filings;

- refusal of the FDA to accept data from clinical trials in affected geographies; and
- delays or difficulties in completing research required to support our pending patent applications.

These and other disruptions in our operations and the global economy could negatively impact our business, operating results and financial condition.

Our Phase 1b/2a clinical trial in patients with pulmonary sarcoidosis was negatively affected by the ongoing COVID-19 pandemic. In 2020, many clinical trial sites in this clinical trial temporarily suspended dosing of previously-enrolled patients and/or enrollment of new patients and some patients discontinued from the trial. While we completed this clinical trial, the availability of results from this clinical trial was delayed until September 2021.

Additionally, under the terms of the Kyorin Agreement, we rely on Kyorin to fund all research, development, regulatory, marketing and commercialization activities in Japan. If Kyorin's operations are limited due to a COVID-19 outbreak in Japan or in other regions where Kyorin operates or relies on third party operations, the development of efzofitimod in Japan may be significantly delayed and adversely affected, which may in turn delay or limit our receipt of any additional payments under the Kyorin Agreement.

Further, we currently rely, and expect to continue to rely, on third parties to conduct some or all aspects of product manufacturing, protocol development, and research and preclinical and clinical testing with respect to our product candidates. While many materials on which we rely may be obtained by more than one supplier, port closures, travel bans and other restrictions resulting from the ongoing COVID-19 pandemic may disrupt our supply chain or limit our ability to obtain sufficient materials to conduct our operations.

As a result of these events and uncertainties, we may need to obtain additional funding through a combination of equity offerings, grant funding, collaborations, strategic partnerships and/or licensing arrangements, and potentially through debt financings, if available on acceptable terms or at all. We may be unable to raise additional funds on acceptable terms or at all. As a result of the ongoing COVID-19 pandemic and actions taken to slow its spread, the global credit and financial markets have experienced volatility and disruptions, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates, inflation and uncertainty about economic stability. If the equity and credit markets deteriorate, it may make any necessary debt or equity financing more difficult, more costly and more dilutive. The impact of the ongoing COVID-19 pandemic on capital markets may affect the availability, amount and type of financing available to us in the future. If we are unable to raise additional funds, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market our product candidates even if we would otherwise prefer to develop and market such product candidates ourselves.

COVID-19 and actions taken to reduce its spread continue to rapidly evolve, including the emergence of new variants and additional actions taken in response to their spread. The extent to which the ongoing COVID-19 pandemic may impede the development of our product candidates, reduce the productivity of our employees, disrupt our supply chains, delay our clinical trials, reduce our access to capital or limit our business development activities, will depend on future developments, which are highly uncertain and cannot be predicted with confidence.

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 principal members of our executive team, the loss of whose services may adversely impact the achievement of our objectives. While we have entered into employment agreements with each of our executive officers, any of them could leave our employment at any time, as all of our employees are "at will" employees. Recruiting and retaining other qualified employees, consultants and advisors for our business, including scientific and technical personnel, will also be critical to our success.

There is currently an extreme shortage of skilled personnel in our industry, which is likely to continue. As a result, competition for skilled personnel is very intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for individuals with similar skill sets. In addition, the available pool of skilled employees may be further reduced if immigration laws change in a manner that increases restrictions on immigration. Further, failure to succeed in preclinical studies or clinical trials may make it more challenging to recruit and retain qualified personnel. The inability to recruit or loss of the services of any executive, key employee, consultant or advisor may impede the progress of our research, development and commercialization objectives.

We may undertake internal restructuring activities in the future that could result in disruptions to our business or otherwise materially harm our results of operations or financial condition.

From time to time we may undertake internal restructuring activities as we continue to evaluate and attempt to optimize our cost and operating structure in light of developments in our business strategy and long-term operating plans. For example, we implemented a corporate restructuring and program prioritization plan in May 2018 that included a reduction in our workforce. Any such restructuring activities may result in write-offs or other restructuring charges. There can be no assurance that any restructuring activities that we have undertaken or undertake in the future will achieve the cost savings, operating efficiencies or other benefits that we may initially expect. Restructuring activities may also result in a loss of continuity, accumulated knowledge and inefficiency during transitional periods and thereafter. In addition, internal restructurings can require a significant amount of time and focus from management and other employees, which may divert attention from commercial operations. If any internal restructuring activities we have undertaken or undertake in the future fail to achieve some or all of the expected benefits therefrom, our business, results of operations and financial condition could be materially and adversely affected.

We are subject to a variety of risks associated with international operations that could materially adversely affect our business.

We currently conduct research activities through Pangu BioPharma Limited, in collaboration with the Hong Kong University of Science and Technology. Additionally, we have conducted clinical trials in the European Union (EU) and in Australia and may conduct future clinical trials internationally. Our partner, Kyorin, conducted an efzofitimod Phase 1 clinical trial in healthy volunteers in Japan. If any of our product candidates are approved for commercialization outside of the United States, we expect to either use our own sales organization or selectively enter into agreements with third parties to market our products on a worldwide basis or in more limited geographical regions, as with Kyorin and efzofitimod in Japan. We are, and we expect that we will continue to be, subject to a variety of risks related to international operations, including, but not limited to: different regulatory requirements for approval of drugs and biologics in foreign countries; reduced or uncertain protection for intellectual property; unexpected changes in tariffs, trade barriers and regulatory requirements; economic weakness, including inflation, or political instability in particular foreign economies and markets; compliance with tax, employment, immigration and labor laws for employees living or traveling abroad; foreign currency fluctuations, which could result in reduced revenues, and other obligations incident to doing business in another country; and the global impacts of the ongoing COVID-19 pandemic.

Any failure to continue our international operations or to commercialize our product candidates outside of the United States may impair our ability to generate revenues and harm our business, prospects and results of operations.

Our employees, principal investigators, consultants and commercial partners may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of fraud or other misconduct by our employees, principal investigators, consultants and commercial partners. Misconduct by these parties could include intentional failures to comply with the regulations of the FDA and non-U.S. regulators, provide accurate information to the FDA and non-U.S. regulators, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. 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. Such misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in significant regulatory sanctions and cause serious harm to our reputation. We have adopted a code of business conduct and ethics applicable to all of our employees, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

We face potential product liability, and, if successful claims are brought against us, we may incur substantial liability and costs. If the use of our product candidates harm patients, or is perceived to harm patients even when such harm is unrelated to our product candidates, our regulatory approvals could be revoked or otherwise negatively impacted and we could be subject to costly and damaging product liability claims.

The use of our product candidates in clinical trials and the sale of any products for which we obtain marketing approval exposes us to the risk of product liability claims. Product liability claims might be brought against us by patients, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. There is a risk that our product candidates may induce adverse events. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- impairment of our business reputation;

- withdrawal of clinical trial participants;
- costs due to related litigation;
- distraction of management's attention from our primary business;
- substantial monetary awards to patients or other claimants;
- the inability to commercialize our product candidates; and
- decreased demand for our product candidates, if approved for commercial sale.

We carry product liability insurance for our clinical trials covering $10.0 million per occurrence and up to $10.0 million in the aggregate, subject to certain deductibles and exclusions. Although we believe the amount of our insurance coverage is typical for companies similar to us in our industry, we may not have adequate insurance coverage or be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. If and when we obtain marketing approval for product candidates, we intend to expand our insurance coverage to include the sale of commercial products; however, we may be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. On occasion, large judgments have been awarded in class action lawsuits based on drugs or medical treatments that had unanticipated adverse effects. A successful product liability claim or series of claims brought against us could cause our stock price to decline and adversely affect our reputation and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business.

Patients with the diseases targeted by our product candidates are often already in severe and advanced stages of disease and may have both known and unknown significant pre-existing and potentially life-threatening health risks. During the course of treatment, patients may suffer adverse events, including death, for reasons that may be related to our product candidates. Such events could subject us to costly litigation, require us to pay substantial amounts of money to injured patients, delay, negatively impact or end our opportunity to receive or maintain regulatory approval to market our products, or require us to suspend or abandon our commercialization efforts. Even in a circumstance in which we do not believe that an adverse event is related to our products, the investigation into the circumstance may be time-consuming or inconclusive. These investigations may interrupt our sales efforts, delay our regulatory approval process in other countries, or impact and limit the type of regulatory approvals our product candidates receive or maintain. As a result of these factors, a product liability claim, even if successfully defended, could have a material adverse effect on our business, financial condition or results of operations.

We are subject to stringent and changing privacy laws, regulations and standards as well as policies, contracts and other obligations related to data privacy and security, as well as federal and state healthcare fraud and abuse laws. Our actual or perceived failure to comply with such obligations could have a material adverse effect on our business and financial condition including a disruption of clinical trials or commercialization of products.

We collect, receive, store, process, use, generate, transfer, disclose, make accessible, protect and share (Process or Processing) personal information and other sensitive information, including information we or our third party partners (such as CROs and clinical trial sites) collect about patients and healthcare providers in connection with clinical trials (Process or Processing) necessary to operate our business, for legal and marketing purposes, and for other business-related purposes.

Therefore, we are, or may become, subject to data privacy and security laws, regulations, and industry standards as well as policies, contracts and other obligations that apply to the Processing of personal data both by us and on our behalf (collectively, Data Protection Requirements). The number and scope of the Data Protection Requirements are changing, subject to differing applications and interpretations, and may be inconsistent between jurisdictions. New Data Protection Requirements may be proposed or enacted. Although we endeavor to comply with all Data Protection Requirements, we may at times fail (or be perceived to have failed) to do so. Moreover, 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, such as a CRO or clinical trial site, to comply with Data Protection Requirements could result in adverse effects, including inability to or interruption in our ability to operate our business and proceedings against us by governmental entities or others.

Additionally, if we or the third parties upon which we rely fail, or are perceived to have failed, to address or comply with Data Protection Requirements, this could result in government enforcement actions against us that could include investigations, fines, penalties, audits and inspections, additional reporting requirements and/or oversight, temporary or permanent bans on all or some Processing of personal data, orders to destroy or not use personal data, and imprisonment of company officials. Further, individuals or other relevant stakeholders could bring a variety of claims against us for our actual or perceived failure to comply with the Data Protection Requirements. Any of these events could have a material adverse effect on our reputation, business, or financial condition, and could lead to a loss of actual or prospective customers, collaborators or partners; interrupt or stop clinical trials; result in an inability to Process personal data or to operate in certain jurisdictions; limit our ability to develop or commercialize our products; require us to revise or restructure our operations; or otherwise materially adversely affect our operations (each, a Material Adverse

Impact). Additionally, given the breadth and evolving nature of Data Protection Requirements, preparing for and complying with these requirements is rigorous, time-intensive and requires significant resources and a review of our technologies, systems and practices, as well as those of any third-party collaborators, service providers, contractors or consultants that Process personal data on our behalf.

Additionally, our operations may be subject to various federal and state healthcare laws, including but not limited to the Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, as well as transparency laws regarding payments or other items of value provided to healthcare providers. These laws may impact, among other things, our research, proposed sales, marketing and education programs. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. If our operations are found to be in violation of any of these laws, we may be subject to penalties, including significant administrative civil and criminal penalties, damages, fines, disgorgement, imprisonment, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, additional reporting requirements and regulatory oversight and the curtailment or restructuring of our operations, any of which could result in a Material Adverse Impact.

In addition, we may become subject to an increasing number of foreign privacy laws. For example, the European Union's (EU) General Data Protection Regulation (EU GDPR) regulates the collection and use of personal data in the EU. The GDPR covers any business, regardless of its location, that provides goods or services to residents in the EU and, thus, could incorporate our activities in EU member states. The GDPR imposes strict requirements on controllers and processors of personal data, including special protections for "sensitive information," which includes health and genetic information of individuals residing in the EU. Failure to comply with the requirements of the EU GDPR may result in warning letters, litigation, orders banning the processing of personal data, mandatory audits and financial penalties, including fines of up to 4% of global revenues, or €20,000,000, whichever is greater.

Certain jurisdictions have enacted data localization laws and cross-border personal data transfer laws, which could make it more difficult to transfer information across jurisdictions (such as transferring or receiving personal data that originates in the EU or in other foreign jurisdictions). Existing mechanisms that facilitate cross-border personal data transfers may change or be invalidated. For example, absent appropriate safeguards or other circumstances, the EU GDPR generally restricts the transfer of personal data to countries outside of the European Economic Area ("EEA") that the European Commission does not consider to provide an adequate level of data privacy and security, such as the United States. The European Commission released a set of "Standard Contractual Clauses" ("SCCs") that are designed to be a valid mechanism to facilitate personal data transfers out of the EEA to these jurisdictions. Currently, these SCCs are a valid mechanism to transfer personal data outside of the EEA, but there exists some uncertainty regarding whether the SCCs will remain a valid mechanism. Additionally, the SCCs impose additional compliance burdens, such as conducting transfer impact assessments to determine whether additional security measures are necessary to protect the at-issue personal data.

In addition, Switzerland and the UK similarly restrict personal data transfers outside of those jurisdictions to countries such as the United States that do not provide an adequate level of personal data protection, and certain countries outside Europe (e.g. Russia, China, Brazil) have also passed or are considering laws requiring local data residency or otherwise impeding the transfer of personal data across borders, any of which could increase the cost and complexity of doing business. If we cannot implement a valid compliance mechanism for cross-border data transfers, we may face increased exposure to regulatory actions, substantial fines, and injunctions against processing or transferring personal data from Europe or other foreign jurisdictions. 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 abroad; limiting our ability to collaborate with parties that are subject to such cross-border data transfer or localization laws; or requiring us to increase our personal data processing capabilities and infrastructure in foreign jurisdictions at significant expense. 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. For example, California enacted the California Consumer Privacy Act (CCPA), which creates new individual privacy rights for California consumers (as defined in the law) and places increased privacy and security obligations on entities handling certain personal data of consumers or households. Aspects of the CCPA and its interpretation and enforcement remain uncertain. In addition, it is anticipated that the CCPA will be expanded on January 1, 2023, when the California Privacy Rights Act of 2020 (CPRA) becomes operative. The CPRA will, among other things, give California residents the ability to limit use of certain sensitive personal information, further restrict the use of cross-contextual advertising, establish restrictions on the retention of personal information, expand the types of data breaches subject to the CCPA's private right of action, and establish a new California Privacy Protection Agency to implement and enforce the new law. Although there are limited exemptions for clinical trial data under the CCPA, the CCPA and other similar laws could impact our business activities depending on how it is interpreted. In addition, other states have enacted or proposed data privacy laws, which could further complicate the legal landscape and increase compliance costs. For example, Virginia recently passed its Consumer Data Protection Act, and Colorado recently passed the Colorado Privacy Act, both of which differ from the CPRA and become effective in 2023.

Unfavorable global economic conditions could adversely affect our business, financial condition or results of operations.

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. For example, the global financial crisis caused volatility and disruptions in the capital and credit markets. In March 2017, the U.K. government provided official legal notification to the EU that the U.K. will exit the EU (commonly referred to as Brexit), which could lead to a period of considerable uncertainty, particularly in relation to global financial markets which in turn could adversely affect our ability to raise additional capital. In addition, due to the ongoing COVID-19 pandemic, the global credit and financial markets have recently experienced extreme volatility and disruptions, including diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates, inflation and uncertainty about economic stability. A severe or prolonged economic downturn, such as the global financial crisis, could result in a variety of risks to our business, including inability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could also strain our CDMOs, possibly resulting in supply disruption. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

We or the third parties upon whom we depend may be adversely affected by earthquakes, droughts, floods, fires, hurricanes or other natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

We are located in San Diego, California and our manufacturing activities are conducted by CDMOs at various locations in the United States. We conducted our Phase I clinical trial for efzofitimod in Australia and we have a subsidiary in Hong Kong. Some of these geographic locations have in the past experienced natural disasters, including severe earthquakes. Earthquakes, droughts, floods, fires, hurricanes, disease epidemics or other natural disasters could severely disrupt our operations, and have a material adverse effect on our business, results of operations, financial condition and prospects. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our facilities, that damaged critical infrastructure, such as the manufacturing facilities of our CDMOs, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place currently are limited and are unlikely to prove adequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, as well as limits on our insurance coverage, which could have a material adverse effect on our business, prospects, financial condition and results of operations.

Risks related to the commercialization of our product candidates

If we are unable to establish sales, marketing and distribution capabilities or enter into agreements with third parties to market and sell our product candidates, we may be unable to generate any revenues.

We do not currently have any infrastructure for the sales, marketing and distribution of pharmaceutical products. In order to market our product candidates, if approved by the FDA or any other regulatory body, we must build our sales, marketing, distribution, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. 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.

If we enter into arrangements or collaborations 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, sell or distribute any medicines 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. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our medicines 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.

We rely on third-party manufacturers to produce our product candidates, but we have not entered into agreements with any such manufacturers to support commercialization.

We have not yet secured manufacturing capabilities for commercial quantities of any of our product candidates. Although we intend to rely on third-party manufacturers for commercialization, we have not yet entered into a long-term commercial supply agreement to support full scale commercial production, and we or our CDMOs may be unable to process validation activities necessary to enter into commercial supply agreements or otherwise negotiate agreements with the manufacturers to support our commercialization activities at commercially reasonable terms.

We may run into technical or scientific issues related to development or manufacturing that we may be unable to resolve in a timely manner or with available funds. For example, we recently engaged an additional CDMO to manufacture efzofitimod bulk drug substance and will need to complete a technology transfer and validation process before the new CDMO will be able to produce additional bulk drug substance for our clinical trials or otherwise. The new CDMO has not previously manufactured efzofitimod bulk drug substance, which subjects us to heighted risks that it will experience delays in validating the manufacturing process. If the new CDMO experiences such delays, particularly delays in producing efzofitimod in compliance with cGMP regulations, we could be forced to delay future clinical trials or the submission of regulatory approval applications to the FDA. In addition, due to the fact that all prior cGMP batches of efzofitimod, including those that we intend to use in an initial pivotal trial, have been produced by our existing CDMO, we may be required to complete comparability studies prior to using efzofitimod produced at the new CDMO's facilities in subsequent clinical trials or submitting regulatory approval applications to the FDA. If we are unable to demonstrate such comparability to the satisfaction of the FDA, it may result in delays to future clinical trials or a deficiency in future regulatory applications. If we or our CDMOs are unable to scale the manufacturing process to produce commercial quantities of our product candidates, or our CDMOs do not pass required regulatory pre-approval inspections, our commercialization efforts will be harmed.

In addition, any significant disruption in our relationships with our CDMOs could harm our business. There are a relatively small number of potential manufacturers for our product candidates, and such manufacturers may not be able to supply our drug products at the times we need them or on commercially reasonable terms. Any disruption to our relationship with our current CDMOs and any manufacturers that we contract with in the future will result in delays in our ability to complete the clinical development of, or to commercialize, our product candidates, and may require us to incur additional costs.

We face intense competition and rapid technological change and the possibility that our competitors may develop therapies that are more advanced or effective than ours, which may adversely affect our financial condition and our ability to successfully commercialize our product candidates.

The biotechnology and pharmaceutical industries are intensely competitive and subject to rapid and significant technological change. We have competitors both in the United States and internationally, including major multi-national pharmaceutical companies, biotechnology companies and universities and other research institutions. Although we believe we are the only company engaged in the discovery and development of therapeutics based on novel functions of tRNA synthetases and NRP2 biology, we are aware of other companies that could compete with our product candidate, efzofitimod for the treatment of pulmonary sarcoidosis and other ILD.

Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff and experienced marketing and manufacturing organizations. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or licensing on an exclusive basis, products that are more effective, safer, more convenient or less costly than any product candidate that we may develop, or achieve earlier patent protection, regulatory approval, product commercialization and market penetration than us. Additionally, technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors.

The commercial success of any current product candidate or future product candidates will depend upon the degree of market acceptance by physicians, patients, third-party payors and others in the medical community.

Even with the requisite approval from the FDA and comparable foreign regulatory authorities, the commercial success of our product candidates will depend in part on the medical community, patients, and third-party payors accepting our product candidates as medically useful, cost-effective, and safe. Any product that we bring to the market may not gain market acceptance by physicians, patients, third-party payors and others in the medical community. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable.

Even if a potential product displays a favorable efficacy and safety profile in preclinical studies and clinical trials, market acceptance of the product will not be known until after it is launched. Our efforts to educate the medical community and third-party payors on the benefits of the product candidates may require significant resources and may never be successful. Such efforts to educate the marketplace may require more resources than are required by the conventional technologies marketed by our competitors, and our competitors may have substantially greater resources or brand recognition to effectively market their products. If our product candidates are approved but fail to achieve an adequate level of acceptance by physicians, patients, third-party payors, and others in the medical community, we will not be able to generate sufficient revenue to become or remain profitable.

The insurance coverage and reimbursement status of newly-approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for new or current products could limit our ability to market those products and decrease our ability to generate revenue.

The availability and extent of coverage and adequate reimbursement by third-party payors, including government health administration authorities, private health coverage insurers, managed care organizations and other third-party payors is essential for most patients to be able to afford expensive treatments. Sales of any of our product candidates that receive marketing approval will depend substantially, both in the United States and internationally, on the extent to which the costs of such product candidates will be covered and reimbursed by third-party payors. If reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize an adequate return on our investment

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, the principal decisions about reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services (CMS), as CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payors often follow CMS with respect to coverage policy and payment limitations in setting their own reimbursement policies. It is difficult to predict what CMS will decide with respect to reimbursement for fundamentally novel products such as ours, as there is no body of established practices and precedents for these new products. One third-party payor's determination to provide coverage for a product candidate does not assure that other payors will also provide coverage for the product candidate. Further, no uniform policy for coverage and reimbursement exists in the United States, and coverage and reimbursement can differ significantly from payor to payor. As a result, the coverage determination process is often time-consuming and costly. This process will require us to provide scientific and clinical support for the use of our products to each third-party payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance. Reimbursement agencies in Europe may be more conservative than third-party payors in the United States. For example, a number of cancer drugs have been approved for reimbursement in the United States, but have not been approved for reimbursement in certain European countries. There may be significant delays in obtaining reimbursement for newly approved medicines, and our inability to promptly obtain coverage and profitable payment rates from third-party payors for any approved medicines could have a material adverse effect on our business, prospects, financial condition and results of operations.

Outside the United States, international sales are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost-containment initiatives in Europe, Canada, and other countries has and will continue to put pressure on the pricing and usage of our product candidates. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. In general, the prices of medicines under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for medicines, but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our products may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenues and profits. Net prices for medicines may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that currently restrict imports of medicines from countries where they may be sold at lower prices than in the United States.

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 level of reimbursement for new products and, as a result, they may not cover or provide adequate payment for our product candidates. For example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010 (collectively, the ACA) was passed in March 2010, and substantially changed the way healthcare is financed by both governmental and private insurers, and continues to significantly impact the U.S. pharmaceutical industry. There have been executive, judicial and congressional challenges to certain aspects of the ACA. While Congress has not passed comprehensive repeal legislation, it has enacted laws that modified certain provisions of the ACA such as removing penalties, starting January 1, 2019, for not complying with the ACA's individual mandate to carry health insurance. In addition, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the ACA-mandated "Cadillac" tax on high-cost employer-sponsored health coverage and medical device tax and, effective January 1, 2021, also eliminated the health insurer tax. On June 17, 2021 the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the ACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. Thus, the ACA will remain in effect in its current form. Further, prior to the U.S. Supreme Court ruling, on January 28, 2021, President Biden issued an executive order that initiated a special enrollment period for purposes of obtaining health insurance coverage through the ACA marketplace, which began on February 15, 2021 and remained open through August 15, 2021. 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 any such challenges and the healthcare reform measures of the Biden administration will impact the ACA and our business.

In addition, there 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 presidential executive orders, congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. For example, on July 24, 2020 and September 13, 2020, President Trump announced several executive orders related to prescription drug pricing that attempt to implement several of the Trump administration's proposals. The FDA concurrently released a final rule and guidance in September 2020, implementing a portion of the importation executive order providing pathways for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020, the U.S. Department of Health and Human Services (HHS) finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of the rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which have also been delayed until January 1, 2023. On November 20, 2020, CMS issued an interim final rule implementing President Trump's Most Favored Nation (MFN) executive order, which would tie Medicare Part B payments for certain physician-administered drugs to the lowest price paid in other economically advanced countries, effective January 1, 2021. As a result of litigation challenging the MFN model, on December 27, 2021, CMS published a final rule that rescinds the MFN model interim final rule. 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 as well as potential administrative actions HHS can take to advance these principles. No legislation or administrative actions have been finalized to implement these principles. In addition, Congress is considering additional health reform measures. 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 health reform measures. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, it is possible that additional governmental action is taken in response to the ongoing COVID-19 pandemic.

In addition, drug prices are under significant scrutiny in the markets in which our products may be sold. Drug pricing and other health care costs continues to be subject to intense political and societal pressures which we anticipate will continue and escalate on a global basis. If coverage and reimbursement is available only to limited levels, we may not be able to successfully commercialize our product candidates for which we obtain marketing approval. As a result, we may have difficulty raising capital and our results of operations may be adversely impacted.

Risks related to the ownership of our common stock

The market price of our common stock historically has been highly volatile and is likely to continue to be volatile, and you could lose all or part of your investment.

The market price of our common stock has been volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. In addition to the factors discussed in this "Risk Factors" section and elsewhere in this Annual Report, these factors include:

- effects of the ongoing COVID-19 pandemic on our business operations or financial condition;
- adverse results or delays in preclinical studies or clinical trials;
- manufacturing sufficient quantities of product candidates for use in clinical trials;
- the imposition of a clinical hold on our product candidates or our inability to cause the clinical hold to be lifted;
- any delay in filing an investigational new drug (IND) or BLA for any of our product candidates and any adverse development or perceived adverse development with respect to the FDA's review of that IND or BLA;
- failure of our strategic partners to perform under our collaborations or early termination of collaborations;
- failure to successfully develop and commercialize our product candidates;
- limited market sizes and pricing for our product candidates;
- failure by us or our licensors to prosecute, maintain or enforce intellectual property rights covering our product candidates and processes;
- changes in laws or regulations applicable to current or future products;

- inability to obtain adequate product supply for our product candidates or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- introduction of new products, services or technologies by our competitors;
- inability to obtain additional capital;
- failure to meet or exceed financial or operational projections we may provide to the public;
- failure to meet or exceed the financial or operational projections of the investment community;
- the perception of the biopharmaceutical industry by the public, politicians, legislatures, regulators and the investment community;
- significant acquisitions, strategic partnerships, joint ventures or capital commitments by us or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent or stockholder litigation;
- if securities or industry analysts issue an adverse or misleading opinion regarding our common stock;
- changes in the market valuations of similar companies;
- changes in the structure of healthcare payment systems;
- general market or macroeconomic conditions;
- sales of our common stock by us or our stockholders in the future;
- a potential additional reverse stock split if we are unable to maintain a stock price above $1.00 per share of common stock; and
- trading volume of our common stock.

In addition, companies trading in the stock market in general, and on the Nasdaq Capital Market and biotechnology companies in particular, have experienced extreme price and volume fluctuations, and we have in the past experienced volatility that has been unrelated or disproportionate to our operating performance. From January 1, 2020 through November 9, 2021 the closing price of our common stock has ranged between $2.17 and $12.48 per share. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance.

Our executive officers, directors, 5% holders and their affiliates currently own a significant percentage of our stock and will be able to exert significant control over matters submitted to stockholders for approval.

As of March 10, 2022, based on the latest information available to us, our executive officers, directors, holders known by us to own 5% of our voting stock and their affiliates own approximately 42.5% of our voting stock. Therefore, our executive officers, directors, holders known by us to own 5% of our voting stock and their affiliates will have the ability to influence us through their ownership positions and may be able to determine all matters requiring stockholder approval. For example, these stockholders, acting together, may be able to control elections of directors, amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may believe are in your best interest as one of our stockholders.

Future sales and issuances of equity securities could result in dilution to our stockholders, impose restrictions or limitations on our business and could cause our stock price to fall.

We will need additional capital in the future to continue our planned operations, and we may seek additional funding through a combination of equity offerings, debt, grant funding, collaborations, strategic partnerships and/or licensing arrangements.

In September 2021, we completed an underwritten follow-on public offering of 10,781,250 shares of our common stock, including the full exercise of the underwriters' option to purchase additional shares, at a price to the public of $8.00 per share. The total net proceeds from the offering were approximately $80.6 million, after deducting underwriting discounts, commissions and offering expenses payable by us.

In September 2020, we entered into a common stock purchase agreement (Purchase Agreement) with Aspire Capital Fund, LLC (Aspire Capital), which provides that, upon the terms and subject to the conditions and limitations set forth therein, Aspire Capital is committed to purchase up to an aggregate of $20.0 million of shares of our common stock at our request from time to time during the 30 month term of the Purchase Agreement. Concurrently with entering into the Purchase Agreement, we also entered into a registration rights agreement with Aspire Capital, in which we agreed to file one or more registration statements, as permissible and necessary to register under the Securities Act, as amended, for the resale of the shares of our common stock that have been and may be issued to Aspire Capital under the Purchase Agreement. For the year ended December 31, 2021, we sold an aggregate of 3,000,000 shares of common stock at an average price of $5.09 per share for net proceeds of $15.2 million under this Purchase Agreement. We may sell the remaining $4.8 million in the future under the Purchase Agreement.

In March 2021, we entered into a Capital on Demand™ Sales Agreement with JonesTrading Institutional Services LLC (JonesTrading) for a new at-the-market offering (ATM Offering Program), pursuant to which we can sell from time to time, at our option, up to an aggregate of $25.0 million of shares of our common stock through JonesTrading, as sales agent or principal. JonesTrading is entitled to a commission at a fixed rate equal to up to 3% of the gross proceeds. For the year ended December 31, 2021, we sold an aggregate of 986,267 shares of common stock at an average price of $4.75 per share for net proceeds of $4.4 million under the ATM Offering Program.

These financing activities may have an adverse effect on our stockholders' rights, the market price of our common stock and on our operations, and may require us to relinquish rights to some of our technologies, intellectual property or product candidates, issue additional equity or debt securities, or otherwise agree to terms unfavorable to us.

In addition, sales of a substantial number of shares of our common stock by our existing stockholders in the public market or the perception that these sales might occur, could depress the market price of our common stock and could impair our ability to raise capital through the sale of additional equity securities. Any sales of securities by these stockholders could have a material adverse effect on the trading price of our common stock, even if there is no relationship between such sales and the performance of our business.

We have also registered or plan to register all common stock that we may issue under our employee benefits plans as well as shares of common stock underlying options to purchase shares of our common stock that were granted as inducement grants. As a result, once registered, these shares can be freely sold in the public market upon issuance, subject to restrictions under the securities laws. In addition, our directors and executive officers may establish programmed selling plans under Rule 10b5-1 of the Exchange Act for the purpose of effecting sales of our common stock. If any of these events cause a large number of our shares to be sold in the public market, the sales could reduce the trading price of our common stock and impede our ability to raise future capital.

Our ability to use our net operating losses to offset future taxable income may be subject to certain limitations.

We have incurred substantial losses during our history, we do not expect to become profitable in the near future and we may never achieve profitability. Net operating loss carryforwards (NOLs) that expire unused will be unavailable to offset future income tax liabilities. Under current law, federal net operating losses incurred in tax years beginning after December 31, 2017, may be carried forward indefinitely, but the deductibility of such federal NOLs in tax years beginning after December 31, 2020, is limited to 80% of taxable income.

In addition, under Section 382 of the Internal Revenue Code of 1986, as amended (Code) a corporation that undergoes an "ownership change" (as defined under Section 382 of the Code and applicable Treasury Regulations) is subject to limitations on its ability to utilize its pre-change NOLs to offset post-change taxable income. We have experienced ownership changes in the past, and may experience future ownership changes, under Section 382 of the Code that could affect our ability to utilize our NOLs to offset our income. Furthermore, our ability to utilize NOLs of companies that we may acquire in the future may be subject to limitations. There is also a risk that due to regulatory changes, such as suspensions on the use of NOLs or other unforeseen reasons, portions of our existing NOLs could expire or otherwise be unavailable to reduce future income tax liabilities, including for state tax purposes. For these reasons, we may not be able to utilize a material portion of our NOLs, even if we attain profitability, which could potentially result in increased future tax liability to us and could adversely affect our operating results and financial condition.

We do not intend to pay dividends on our common stock, and therefore any returns will be limited to the value of our stock.

We have never declared or paid any cash dividends on our common stock. We anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock.

In addition, future debt instruments may materially restrict our ability to pay dividends on our common stock. Any future determination related to 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, tax considerations, legal or contractual restrictions,

business prospects, the requirements of current or then-existing debt instruments, general economic conditions and other factors our board of directors may deem relevant.

Provisions in our amended and restated certificate of incorporation and amended and restated bylaws, as well as provisions of Delaware law, could make it more difficult for a third party to remove our current management, acquire us or increase the cost of acquiring us, even if doing so would benefit our stockholders.

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

- authorize "blank check" preferred stock, which could be issued by our board of directors without stockholder approval and may contain voting, liquidation, dividend and other rights superior to our common stock;
- create a classified board of directors whose members serve staggered three-year terms;
- specify that special meetings of our stockholders can be called only by our board of directors, the chairperson of our board of directors, our chief executive officer or our president;
- prohibit stockholder action by written consent;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;
- provide that our directors may be removed only for cause;
- 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;
- specify that no stockholder is permitted to cumulate votes at any election of directors;
- expressly authorize our board of directors to modify, alter or repeal our amended and restated bylaws; and
- require supermajority votes of the holders of our common stock to amend specified provisions of our amended and restated certificate of incorporation and amended and restated bylaws.

These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in 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, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us.

Any provision of our amended and restated certificate of incorporation or amended and restated bylaws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

Our amended and restated bylaws provide that the Court of Chancery of the State of Delaware is the exclusive forum for certain disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our amended and restated bylaws provide that the Court of Chancery of the State of Delaware will be the sole and exclusive forum for (i) any derivative action or proceeding brought on our behalf, (ii) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers or employees to our company or our stockholders, (iii) any action asserting a claim against our company arising pursuant to any provision of the Delaware General Corporation Law or our amended and restated certificate of incorporation or bylaws, or (iv) any action asserting a claim against our company governed by the internal affairs doctrine. This choice of forum provision does not apply to suits brought to enforce a duty or liability created by the Securities Act or the Exchange Act, or any other claim for which the federal courts have exclusive jurisdiction.

This choice of forum provision may limit a stockholder's ability to bring certain claims 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, although our stockholders will not be deemed to have waived our compliance with federal securities laws and the rules and regulations thereunder. If a court were to find this choice of forum provision to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our business and financial condition.

General Risk Factors

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

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials or other work-related injuries, this insurance may not provide adequate coverage against potential liabilities. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

If our security measures, or those maintained on our behalf, are compromised now, or in the future, or the security, confidentiality, integrity or availability of our information technology, software, services, networks, communications or data is compromised, limited or fails, this could result in a Material Adverse Impact.

In the ordinary course of our business, we may Process (as defined above) proprietary, confidential and sensitive information, including personal data (including key-coded data, health information and other special categories of personal data), intellectual property, trade secrets, and proprietary business information owned or controlled by ourselves or other third parties (collectively, Sensitive Information).

We utilize information technology systems and networks to process, transmit and store electronic information in connection with our business activities. We may also use third-party service providers and subprocessors to help us operate our business and engage in Processing on our behalf or otherwise share Sensitive Information with our partners or other third parties in conjunction with our business. If we, our service providers, partners or other relevant third parties have experienced or in the future experience any security incident(s) that result in any data loss; deletion or destruction; unauthorized access to; loss, unauthorized acquisition, disclosure or exposure of Sensitive Information, or compromise related to the security, confidentiality, integrity or availability of our (or their) information technology, software, services, communications or data (any, a Security Breach), it may result in a Material Adverse Impact (as defined above). For example, the loss of data from completed clinical trials for our product candidates could result in delays in our regulatory approval efforts and significantly increase our costs. Theft of our Sensitive Information could require substantial expenditures to remedy. If we or the third parties upon which we rely experience a Security Breach, we could suffer reputational harm or face litigation or adverse regulatory action, fines, other penalties, business interruption, and diversion of funds. As a result, we could experience Material Adverse Impacts.

As use of digital technologies has increased, cyber incidents, malicious internet-based activity, and online and offline fraud have become prevalent and have increased in frequency and sophistication. These threats come from a variety of sources, including traditional computer "hackers," threat actors, personnel (such as through theft or misuse), sophisticated nation states, and nation state supported actors. Some actors now engage and are expected to continue to engage in cyber-attacks, including without limitation nation state actors for geopolitical reasons and in conjunction with military conflicts and defense activities. During times of war and other major conflicts, we and the third parties upon which we rely may be vulnerable to a heightened risk of these attacks, including cyber-attacks that could materially disrupt our systems and operations, supply chain, and ability to produce, sell and distribute our goods and services. We and the third parties upon which we rely may be subject to a variety of evolving threats, including but not limited to software bugs; malicious code (such as viruses and worms); denial-of-service attacks (such as credential stuffing); advanced persistent threat intrusions; natural disasters; terrorism; war; telecommunication and electrical failures; ransomware attacks; phishing attacks; server malfunction; software or hardware failures; supply-chain attacks; loss of data or other computer assets; and other similar issues. Particularly, ransomware attacks, including those from organized criminal threat actors, nation-states and nation-state supported actors, are becoming increasingly prevalent and severe and can lead to significant interruptions, delays, or outages in our operations, disruption of clinical trials, loss of data (including data related to clinical trials), and other Material Adverse Impacts. To alleviate the financial, operational and reputational impact of a ransomware attack, it may be preferable to make extortion payments, but we may be unwilling or unable to do so (including, for example, if applicable laws or regulations prohibit 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 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 platform, systems and networks or the systems and networks of third parties that support us and our services.

Additionally, due to the ongoing COVID-19 pandemic and the competitive labor market, a significant portion of our workforce works remotely and that has increased the risk to our information technology assets and data. These threats pose a risk to the security of our systems and networks and the confidentiality, availability and integrity of our data. Additionally, future or past business transactions could expose us to additional risks and vulnerabilities, as our systems could be negatively affected by vulnerabilities present in acquired or integrated entities' systems and technologies. While we have implemented security measures designed to protect against Security Breaches, there can be no assurance that we, or any third-party partner, will be successful in preventing cyber-attacks or mitigating their effects. We may be required to expend significant resources, fundamentally change our business activities and practices, or modify our operations, including our clinical trial activities, or information technology in an effort to protect against Security Breaches and to mitigate, detect, and remediate actual and potential vulnerabilities. Applicable Data Protection Requirements (as defined above) may require us to implement specific security measures or use industry-standard or reasonable measures to protect against Security Breaches.

Furthermore, applicable Data Protection Requirements may require us to notify relevant stakeholders of Security Breaches. Such disclosures are costly, and the disclosures or the failure to comply with such requirements could lead to Material Adverse Impacts. There can be no assurance that any limitations or exclusions of liability in our contracts would be enforceable or adequate or would otherwise protect us from liabilities or damages if we fail to comply with Data Protection Requirements related to information security or Security Breaches.

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, if any, will be adequate or otherwise protect us from or adequately mitigate liabilities or damages with respect to claims, costs, expenses, litigation, fines, penalties, business loss, data loss, regulatory actions or Material Adverse Impacts arising out of our Processing operations, privacy and security practices, or Security Breaches we may experience. The successful assertion of one or more large claims against us that exceeds our available insurance coverage, or results in changes to our insurance policies (including premium increases or the imposition of large excess or deductible or co-insurance requirements), could have a Material Adverse Impact.

We are subject to anti-corruption laws in the jurisdictions in which we operate.

We are subject to a number of anti-corruption laws, including the Foreign Corrupt Practices Act of 1977, as amended (FCPA), and various other anti-corruption laws. The FCPA generally prohibits companies and their intermediaries from making improper payments to foreign officials for the purpose of obtaining or keeping business and/or other benefits. Our business relies on approvals and licenses from government and regulatory entities, and as a result, we are subject to certain elevated risks associated with interactions with these entities. Although we have adopted a code of business conduct and ethics that includes provisions governing the interactions of employees with government entities to mitigate these risks, there can be no assurance that this will be successful in preventing violations of anti-corruption laws. If we are not in compliance with anti-corruption laws and other laws governing the conduct of business with government entities (including local laws), we may be subject to criminal and civil penalties and other remedial measures, which could harm our reputation and have a material adverse impact on our business, financial condition, results of operations and prospects. Any investigation of any actual or alleged violations of such laws could also harm our reputation or have an adverse impact on our business, prospects, financial condition and results of operations.

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

As a public company, we have incurred and will continue to incur legal, accounting and other expenses. In addition, the Sarbanes-Oxley as well as rules subsequently implemented by the SEC and The Nasdaq Stock Market have imposed various requirements on public companies. In July 2010, the Dodd-Frank Wall Street Reform and Consumer Protection Act (the Dodd-Frank Act) was enacted. There are significant corporate governance and executive compensation related provisions in the Dodd-Frank Act that require the SEC to adopt additional rules and regulations in these areas such as "say on pay" and proxy access. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business in ways we cannot currently anticipate. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, we expect these rules and regulations to make it more difficult and more expensive for us to maintain director and officer liability insurance and we have been required to incur substantial costs to maintain our current levels of such coverage.

If securities analysts do not publish research or reports about our business or if they publish negative evaluations of our stock, the price of our stock could decline.

The trading market for our common stock relies in part on the research and reports that industry or financial analysts publish about us or our business. If no or few analysts commence coverage or continue coverage of us, the trading price of our stock would likely decrease. If one or more of the analysts covering our business downgrade their evaluations of our stock, the price of our stock could decline. If one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price to decline.

We could be subject to securities class action litigation.

In the past, securities class action litigation has often been brought against companies following a decline in the market price of their securities. This risk is especially relevant for us because pharmaceutical companies have experienced significant stock price volatility. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business and cause our stock price to decline.

We have broad discretion in the use of our cash, cash equivalents and investments and are exposed to risks related to the marketable securities we may purchase.

We have considerable discretion in the application of our existing cash, cash equivalents and investments. We expect to use our existing cash to fund research and development activities and for working capital and general corporate purposes, including funding the costs of operating as a public company. In addition, pending their use, we may invest our existing cash in certain short-term investments, including but not limited to investment-grade, interest-bearing securities. Historically, investment in these securities has been highly liquid and has experienced only very limited defaults. However, volatility in the financial markets in recent years has created additional uncertainty regarding the liquidity and safety of these investments. Additionally, we may use these proceeds for purposes that do not yield a significant return or any return at all for our stockholders.

Item 1B. Unresolved Staff Comments.

Not applicable.

Item 2. Properties.

We lease our headquarters located at 3545 John Hopkins Court, Suite #250, San Diego, California pursuant to a lease agreement that expires on May 15, 2023. The lease covers 20,508 rentable square feet of office and laboratory space. We believe that our facility is sufficient to meet our needs and that suitable additional space will be available as and when needed.

Item 3. Legal Proceedings.

We are not a party to any material legal proceedings at this time. From time to time, we may be subject to various legal proceedings and claims that arise in the ordinary course of our business activities. Although the results of litigation and claims cannot be predicted with certainty, we do not believe we are party to any claim or litigation the outcome of which, if determined adversely to us, would individually or in the aggregate be reasonably expected to have a material adverse effect on our results of operations or financial condition. Regardless of the outcome, litigation can have an adverse effect 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 is traded on the Nasdaq Capital Market under the symbol "LIFE."

Holders of Record

As of March 10, 2022, there were approximately 32 holders of record of our common stock. The approximate number of holders is based upon the actual number of holders registered in our records at such date and excludes holders in "street name" or persons, partnerships, associations, corporations, or other entities identified in security positions listings maintained by depository trust companies.

Dividend Policy

We have never declared or paid any cash dividends on our common 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, tax considerations, legal or contractual restrictions, business prospects, the requirements of current or then-existing debt instruments, general economic conditions and other factors our board of directors may deem relevant.

Securities Authorized for Issuance Under Equity Compensation Plans

Information about our equity compensation plans is incorporated herein by reference to Part III, Item 12 “Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters.”

Recent Sales of Unregistered Securities

During the year ended December 31, 2021, we did not issue or sell any unregistered securities not previously disclosed in a Quarterly Report on Form 10-Q or in a Current Report on Form 8-K.

Issuer Purchases of Equity Securities

We did not repurchase any securities during the three months ended December 31, 2021.

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 and the consolidated financial statements and related notes included elsewhere in this Annual Report on Form 10-K (Annual Report). The following discussion contains forward-looking statements that involve risks and uncertainties. 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 “Part I, Item 1A. Risk Factors.”

Overview

We are a biotherapeutics company engaged in the discovery and development of innovative medicines based on novel biological pathways. We have concentrated our research and development efforts on a newly discovered area of biology, the extracellular functionality and signaling pathways of tRNA synthetases. Built on more than a decade of foundational science on extracellular tRNA synthetase biology and its effect on immune responses, we have built a global intellectual property estate directed to a potential pipeline of protein compositions derived from 20 tRNA synthetase genes and their extracellular targets, such as neuropilin-2 (NRP2).

Our lead therapeutic candidate, efzofitimod (the non-proprietary name for ATYR1923), is a fusion protein comprised of the immunomodulatory domain of histidyl-tRNA synthetase fused to the fragment crystallizable (Fc) region of a human antibody, and serves as a selective modulator of NRP2 that downregulates innate and adaptive immune response in inflammatory disease states. We are developing efzofitimod as a potential disease-modifying therapy for patients with fibrotic lung diseases with high unmet medical need. This includes interstitial lung diseases (ILD), a group of rare immune-mediated disorders that cause progressive fibrosis of the lung. In December 2018, we designed a Phase 1b/2a multiple-ascending dose, double-blind, placebo-controlled clinical trial in patients with pulmonary sarcoidosis, a major form of ILD, to evaluate the safety, tolerability, immunogenicity and steroid-sparing effect of efzofitimod, and conduct other exploratory assessments of efficacy, such as lung function. In September 2021, we announced positive results and clinical proof-of-concept from the Phase 1b/2a clinical trial in 37 patients with pulmonary sarcoidosis. Efzofitimod was safe and well-tolerated at all doses administered with no serious drug-related adverse events or signal of immunogenicity. Additionally, the study demonstrated consistent dose response for efzofitimod on key efficacy endpoints and improvements compared to placebo, including measures of steroid reduction, lung function, pulmonary sarcoidosis symptom measures and inflammatory biomarkers. Based on the results of this study, we met with the U.S. Food and Drug Administration (FDA) in February 2022 and presented these data and our plans for subsequent clinical development and path to registration for efzofitimod for the treatment of pulmonary sarcoidosis. As a result of the meeting, we intend to initiate a planned registrational trial of efzofitimod in the third quarter of 2022. Based on the results of the Phase 1b/2a clinical trial, we believe efzofitimod has potential applications in the treatment of other ILDs, such as chronic hypersensitivity pneumonitis (CHP) and connective tissue disease related ILD (CTD-ILD).

In January 2020, we entered into a collaboration and license agreement (Kyorin Agreement) with Kyorin Pharmaceutical Co., Ltd. (Kyorin) for the development and commercialization of efzofitimod for the treatment of ILD in Japan. Under the Kyorin Agreement, Kyorin received an exclusive right to develop and commercialize efzofitimod in Japan for all forms of ILD, and is obligated to fund all research, development, regulatory, marketing and commercialization activities in Japan. In September 2020,

Kyorin began dosing patients in a Phase 1 clinical trial of efzofitimod (known as KRP-R120 in Japan) and completed the last subject visit in December 2020. The Phase 1 clinical trial, which was conducted and funded by Kyorin, was a placebo-controlled clinical trial to evaluate the safety, pharmacokinetics (PK) and immunogenicity of efzofitimod in 32 healthy Japanese male volunteers. Efzofitimod was observed to be generally well-tolerated with no drug-related serious adverse events, and PK findings were consistent with previous studies of efzofitimod. We received an $8.0 million upfront payment in January 2020 and a $2.0 million milestone payment in January 2021 upon completion of enrollment in the Phase 1 clinical trial, and we are eligible to receive up to an additional $165.0 million in the aggregate upon achievement of certain development, regulatory and sales milestones, as well as tiered royalties ranging from the mid-single digits to mid-teens on net sales in Japan.

In January 2022, the FDA granted efzofitimod an orphan drug designation for the treatment of sarcoidosis.

In parallel with our clinical development of efzofitimod, we have been advancing our discovery pipeline of NRP2 antibodies and tRNA synthetases. In November 2020, we announced ATYR2810 as our lead Investigational New Drug (IND) candidate in oncology from our NRP2 antibody program. ATYR2810 is a fully humanized monoclonal antibody that is designed to specifically and functionally block the interaction between NRP2 and vascular endothelial growth factor (VEGF). NRP2 is a pleiotropic cell surface receptor that is highly expressed on certain tumors and increased NRP2 expression is associated with worse outcomes in many cancers, such as overall survival, metastasis and resistance to targeted therapies. The role of NRP2 and VEGF signaling in the tumor microenvironment and its importance in the progression of certain aggressive cancers is becoming increasingly validated. ATYR2810 is in preclinical development for the potential treatment of certain aggressive cancers where NRP2 is implicated, and we plan to initiate a Phase 1 clinical trial in the second half of 2022.

In March 2020, our subsidiary, Pangu BioPharma Limited (Pangu BioPharma), together with the Hong Kong University of Science and Technology (HKUST) was awarded a grant of approximately $750,000 to build a high-throughput platform for the development of bi-specific antibodies. The project is being funded by the Hong Kong government's Innovation and Technology Commission (ITC) under the Partnership Research Program (PRP). The PRP aims to support research and development projects undertaken by companies in collaboration with local universities and public research institutions. The ITC funded approximately 50% of the total estimated project cost, and we contributed the remaining 50%. The term of the project was initially for two years and in December 2021, due to complications arising from the ongoing COVID-19 pandemic, was extended for an additional six months with no additional costs. In May 2021, we announced that Pangu and HKUST achieved certain milestones for the first year of the project.

In February 2021, we announced two new discovery programs from our tRNA synthetase platform. These programs will investigate the functionality of selected fragments of Alanyl-tRNA synthetase (AARS) and Aspartyl-tRNA synthetase (DARS) in immunology, fibrosis and cancer. We are also advancing our preclinical pipeline of tRNA synthetases and NRP2 targeting candidates through internal research efforts, industry and academic collaborations. The impacts of the ongoing COVID-19 pandemic on our business have included the delay in enrollment of our now completed Phase 1b/2a clinical trial in patients with pulmonary sarcoidosis and the discontinuation of some patients in that trial, temporary closures of portions of our facilities and those of our licensees and collaborators, disruptions or restrictions on our employees' ability to travel and delays in certain research and development activities. Other potential impacts to our business include, but are not limited to disruptions to or delays in other clinical trials, third-party manufacturing supply and other operations, the potential diversion of healthcare resources away from the conduct of clinical trials to focus on pandemic concerns, interruptions or delays in the operations of the FDA or other regulatory authorities, and our ability to raise capital and conduct business development activities.

Liquidity and Capital Resources

We have incurred losses and negative cash flows from operations since our inception. As of December 31, 2021, we had an accumulated deficit of $372.3 million and we expect to continue to incur net losses for the foreseeable future. As of December 31, 2021, we had cash, cash equivalents and available-for-sale investments of $107.9 million. We believe that our current cash, cash equivalents and available-for-sale investments, will be sufficient to meet our material cash requirements from known contractual and other obligations for a period of at least one year from the date of this Annual Report. We believe we will meet longer-term material cash requirements from known contractual and other obligations through a combination of cash, cash equivalents and available-for-sale investments. In addition to the factors discussed under "Material Cash Requirements," our ability to fund our longer-term operating needs will depend on our ability to raise additional funding through equity or debt offerings, grant funding, collaborations, strategic partnerships and/or licensing arrangements, and other factors, including those discussed in Part I. Item 1A. "Risk Factors – We will need to raise additional capital or enter into strategic partnering relationships to fund our operations."

Sources of Cash

From our inception through December 31, 2021, our primary sources of cash have been the sale of equity securities, convertible debt, venture debt, term loans and revenues generated through license and collaboration agreement.

Public Offerings

In September 2021, we completed an underwritten follow-on public offering of 10,781,250 shares of our common stock, including the full exercise of the underwriters' option to purchase additional shares, at a price to the public of $8.00 per share. The total net proceeds from the offering were approximately $80.6 million, after deducting underwriting discounts, commissions and offering expenses payable by us.

In February 2020, we completed an underwritten follow-on public offering of 4,235,294 shares of our common stock at a price to the public of $4.25 per share. In March 2020, the underwriters fully exercised their over-allotment option for the issuance of an additional 635,294 shares of common stock. The total net proceeds from the offering were approximately $18.8 million, after deducting underwriting discounts, commissions and offering expenses payable by us.

At-the-Market Offering Programs

In March 2021, we entered into a Capital on Demand™ Sales Agreement with JonesTrading Institutional Services LLC (JonesTrading) to create an at-the-market offering (ATM Offering Program) under which we may offer and sell shares of our common stock having an aggregate offering price of up to $25.0 million. JonesTrading is entitled to a commission at a commission rate up to 3% of the gross proceeds. For the year ended December 31, 2021, we sold an aggregate of 986,267 shares of common stock at an average price of $4.75 per share for net proceeds of $4.4 million under the JonesTrading ATM Offering Program.

In May 2019, we entered into a sales agreement with H.C. Wainwright & Co., LLC (Wainwright) for an ATM Offering Program under which we could offer and sell shares of our common stock having an aggregate offering price of up to $10.0 million. In November 2020, we amended our sales agreement with Wainwright to increase the amount of the ATM Offering Program to $20.0 million. Wainwright was entitled to a commission at a fixed commission rate equal to 3% of the gross proceeds. In March 2021, the ATM Offering Program with Wainwright automatically terminated upon the issuance and sale of all of the shares having an aggregate offering price of $20.0 million. Under the ATM Offering Program with Wainwright, during 2020, we sold an aggregate of 1,657,075 shares of common stock at an average price of $4.07 per share for net proceeds of $6.4 million. Prior to the termination of the sales agreement with Wainwright, in 2021, we sold an aggregate of 1,988,254 shares of common stock at an average price of $4.99 per share for net proceeds of $9.6 million.

Purchase Agreement

In September 2020, we entered into a common stock purchase agreement (Purchase Agreement) with Aspire Capital Fund, LLC (Aspire Capital), which provides that, upon the terms and subject to the conditions and limitations set forth therein, Aspire Capital is committed to purchase up to an aggregate of $20.0 million of shares of our common stock at our request from time to time during the 30 month term of the Purchase Agreement. Concurrently with entering into the Purchase Agreement, we also entered into a registration rights agreement with Aspire Capital, in which we agreed to file one or more registration statements, as permissible and necessary to register under the Securities Act of 1933, as amended, for the resale of the shares of our common stock that have been and may be issued to Aspire Capital under the Purchase Agreement. For the year ended December 31, 2021, we sold an aggregate of 3,000,000 shares of common stock at an average price of $5.09 per share for net proceeds of $15.2 million under this Purchase Agreement.

Kyorin Agreement Milestone Payments

We received an $8.0 million upfront payment in January 2020 and a $2.0 million milestone payment in January 2021 upon completion of enrollment in the Phase 1 clinical trial, and we are eligible to receive up to an additional $165.0 million in the aggregate upon achievement of certain development, regulatory and sales milestones, as well as tiered royalties ranging from the mid-single digits to mid-teens on net sales in Japan.

HKUST Grant Agreement

In March 2020, our subsidiary, Pangu BioPharma Limited (Pangu BioPharma), together with the Hong Kong University of Science and Technology (HKUST) was awarded a grant of approximately $750,000 to build a high-throughput platform for the development of bi-specific antibodies. The project is being funded by the Hong Kong government's Innovation and Technology Commission (ITC) under the Partnership Research Program (PRP). The PRP aims to support research and development projects undertaken by companies in collaboration with local universities and public research institutions. The ITC funded approximately 50% of the total estimated project cost, and we contributed the remaining 50%.

Cash Flows

The following table sets forth a summary of the net cash flow activity for each of the periods indicated (in thousands):

	Years Ended December 31,		
	2021	**2020**	**2019**
Net cash provided by (used in):			
Operating activities	$ (33,075)	$ (15,301)	$ (20,013)
Investing activities	(91,566)	6,900	4,925
Financing activities	110,025	16,143	1,336
Net change in cash and cash equivalents	$ (14,616)	$ 7,742	$ (13,752)

Operating activities. Net cash used in operating activities was $33.1 million, $15.3 million and $20.1 million for the years ended December 31, 2021, 2020 and 2019, respectively. The net cash used in operating activities in each of these periods was primarily due to our net losses. The primary differences between net cash used in operating activities and our net loss in the year ended December 31, 2021 related to non-cash charges including: $0.5 million for depreciation, $1.6 million for stock-based compensation, $0.8 million for amortization of right-of-use asset, and a $2.6 million increase in our net operating assets and liabilities. The primary differences between net cash used in operating activities and our net loss in the year ended December 31, 2020 related to non-cash charges including: $0.6 million for depreciation, $1.5 million for stock-based compensation, $0.7 million for amortization of right-of-use asset and a $2.3 million increase in our net operating assets and liabilities. The primary differences between net cash used in operating activities and our net loss in the year ended December 31, 2019 related to non-cash charges including: $0.6 million for depreciation, $1.8 million for stock-based compensation, $0.7 million for debt discount accretion and non-cash interest expense, $0.7 million for amortization of right-of-use asset and a $0.2 million decrease in our net operating assets and liabilities.

Investing activities. Net cash provided by (used in) investing activities for the years ended December 31, 2021, 2020 and 2019 was $(91.6) million, $6.9 million and $4.9 million, respectively. The fluctuation in net cash provided by or used in investing activities resulted primarily from the timing differences in investment purchases, sales and maturities, and the fluctuation of our portfolio mix between cash equivalents and investment holdings. The average term to maturity in our investment portfolio as of December 31, 2021 was less than two years.

Financing activities. Net cash provided by financing activities for the year ended December 31, 2021 was $110.0 million and consisted primarily of $80.6 million in proceeds from an underwritten follow-on public offering, net of offering costs, $15.2 million in proceeds from the issuance of common stock through the Purchase Agreement, net of offering costs and $14.1 million proceeds from the ATM Offering Program, net of issuance costs. Net cash provided by financing activities for the year ended December 31, 2020 was $16.1 million and consisted primarily of $18.8 million in proceeds from an underwritten follow-on public offering, net of offering costs, and $6.4 million proceeds from the ATM Offering Program, net of issuance costs, offset in part by $9.1 million of principal payments and final payment on the term loans. Net cash provided by financing activities for the year ended December 31, 2019 was $1.3 million and consisted primarily of $4.4 million in proceeds from the ATM Offering Program, net of issuance costs, and $4.9 million in proceeds from a registered direct offering, net of issuance costs, offset in part by $8.0 million of principal payments on the term loans.

Material Cash Requirements

To date, we have not generated any revenues from product sales. We expect our expenses to increase in connection with our ongoing activities, particularly as we continue to advance efzofitimod in clinical development, including manufacturing and technology transfer activities for efzofitimod, continue IND-enabling studies and manufacturing activities for ATYR2810, continue our research and development activities with respect to other potential therapies based on tRNA synthetase biology and NPR2 biology, and seek marketing approval for product candidates that we may develop. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. We currently have no sales or marketing capabilities and would need to expand our organization to support these activities. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. Our forecast of the period of time through which our financial resources will be adequate to support our operations is a forward-looking statement that involves risks and uncertainties, and actual results could vary materially.

Our future capital requirements are difficult to forecast and will depend on many factors, including:

- the type, number, scope progress, expansions, results, costs and timing of, our clinical trials and preclinical studies for our product candidates or other potential product candidates or indications which we are pursuing or may choose to pursue in the future;
- the costs, timing and outcome of regulatory review of our product candidates;

- delays of our planned clinical trials of efzofitimod and ATYR2810;
- any resulting cost increases as a result of the ongoing COVID-19 pandemic;
- the number and characteristics of product candidates that we pursue;
- the scope, progress, results and costs of preclinical development, and clinical trials for other product candidates;
- the manufacturing of preclinical study and clinical trial materials, including technology transfers to additional contract development and manufacturing organizations (CDMO);
- our ability to maintain existing and enter into new collaboration and licensing arrangements and the timing of any payments we may receive under such arrangements;
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims;
- the costs and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution, for any of our product candidates for which we receive marketing approval; and
- the extent to which we acquire or in-license other products and technologies.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, grant funding, collaborations, strategic partnerships and/or licensing arrangements, and when we are closer to commercialization of our product candidates potentially through debt financings. To the extent we raise additional capital through the sale of equity, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. If we raise additional funds through collaborations, strategic partnerships or licensing arrangements with third parties, we may have to relinquish valuable rights to our product candidates, our other technologies, future revenue streams or research programs or grant licenses on terms that may not be favorable to us. The incurrence of additional indebtedness would increase our fixed payment obligations and may require us to agree to certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. We may be unable to raise additional funds on acceptable terms or at all. As a result of the ongoing COVID-19 pandemic and actions taken to slow its spread, the global credit and financial markets have experienced extreme volatility and disruptions, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. If the equity and credit markets deteriorate, it may make any necessary debt or equity financing more difficult, more costly and more dilutive. If we are unable to raise additional funds, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market our product candidates even if we would otherwise prefer to develop and market such product candidates ourselves.

As of December 31, 2021, our material cash requirements from known contractual and other obligations consisted primarily of a non-cancelable facility lease that is subject to base lease payments, which escalate over the term of the lease, additional charges for common area maintenance and other costs. In July 2018, we entered into a lease amendment that reduced the space we lease from 24,494 square feet to 20,508 square feet and extended the lease term to May 2023. With the lease amendment, we do not have an option to extend the lease. As of December 31, 2021, the aggregate present value of the lease payments was $1.4 million of which $1.0 million will be incurred in 2022 and $0.4 million will be incurred in 2023.

Financial Operations Overview

Organization and Business; Principles of Consolidation

We conduct substantially all of our activities through aTyr Pharma, Inc., a Delaware corporation, at our facility in San Diego, California. aTyr Pharma, Inc. was incorporated in the State of Delaware in September 2005. The consolidated financial statements include our accounts and our 98% majority-owned subsidiary in Hong Kong, Pangu BioPharma, as of December 31, 2021. All intercompany transactions and balances are eliminated in consolidation.

Revenue Recognition

In January 2020, we entered into a collaboration and license agreement with Kyorin for the development and commercialization of efzofitimod for ILD in Japan. Under the Kyorin Agreement, Kyorin received an exclusive right to develop and commercialize efzofitimod in Japan for all forms of ILD. Under the terms of the Kyorin Agreement, Kyorin will fund all research, development, regulatory, marketing and commercialization activities in Japan. In September 2020, Kyorin began dosing of its Phase 1 trial of efzofitimod (known as KRP-R120 in Japan) and completed the last subject visit in December 2020. This achievement triggered a $2.0 million milestone payment, which we received in January 2021. The Phase 1 trial, which was conducted and funded by Kyorin, is a placebo-controlled study to evaluate the safety, PK and immunogenicity of efzofitimod in 32 healthy Japanese male volunteers.

Efzofitimod was observed to be generally well-tolerated with no drug-related serious adverse events and PK findings were consistent with previous studies of efzofitimod. We received an $8.0 million upfront payment and a $2.0 milestone payment and we are eligible to receive an additional $165.0 million in the aggregate upon achievement of certain development, regulatory and sales milestones, as well as tiered royalties ranging from the mid-single digits to mid-teens on net sales in Japan.

For the year ended December 31, 2021, there were no activities that triggered additional license and collaboration agreement revenue while we recognized $10.0 million as license and collaboration agreement revenue for the year ended December 31, 2020 under the Kyorin Agreement.

Research and Development Expenses

To date, our research and development expenses have been related primarily to the development of, and clinical trials for, our product candidates, and to research efforts targeting the potential therapeutic application of other tRNA synthetase-based immunomodulators and, more recently research efforts related to NRP2 biology. These expenses consist primarily of:

- salaries and employee-related expenses, including stock-based compensation and benefits for personnel in research and product development functions;
- costs associated with conducting our preclinical, development and regulatory activities, including fees paid to third-party professional consultants, service providers and our scientific, therapeutic and clinical advisory board;
- costs to acquire, develop and manufacture preclinical study and clinical trial materials;
- costs incurred under clinical trial agreements with clinical research organizations (CROs) and investigative sites;
- costs for laboratory supplies; and
- allocated facilities, depreciation and other allocable expenses.

Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect that the levels of our research and development expenses will continue to increase in future years and will consist primarily of costs related to our clinical development and manufacturing of efzofitimod for patients with pulmonary sarcoidosis, including the costs associated with technology transfer to an additional CDMO of efzofitimod, our preclinical development, planned clinical development and manufacturing of ATYR2810 and other potential therapeutics based on tRNA synthetase biology and NRP2 biology.

We cannot determine with certainty the timing of initiation, the duration or the completion costs of current or future preclinical studies and clinical trials of our product candidates. For instance, as a result of the ongoing COVID-19 pandemic, many clinical trial sites in our completed Phase 1b/2a clinical trial in patients with pulmonary sarcoidosis temporarily suspended dosing of previously-enrolled patients and/or enrollment of new patients and some patients discontinued from the trial.

At this time, due to the inherently unpredictable nature of preclinical and clinical development and given the early stage of our programs, we are unable to estimate with any certainty the costs we will incur or the timelines we will require in the continued development of our product candidates. Clinical and preclinical development timelines, the probability of success and development costs can differ materially from expectations. We anticipate that we will make determinations as to which product candidates to pursue and how much funding to direct to each product candidate on an ongoing basis in response to the results of ongoing and future preclinical studies and clinical trials, regulatory developments and our ongoing assessments as to each product candidate’s commercial potential. In addition, we cannot forecast which programs or product candidates may be subject to future collaborations, when such arrangements will be secured, if at all, and to what degree such arrangements would affect our development plans and capital requirements.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries and related costs for employees in executive, finance and administration, corporate development and administrative support functions, including stock-based compensation expenses and benefits. Other significant general and administrative expenses include accounting, legal services, expenses associated with applying for and maintaining patents, cost of insurance, cost of various consultants, occupancy costs, information systems costs and depreciation.

Critical Accounting Policies and Significant Judgments and Estimates

Our management’s discussion and analysis of financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States. The preparation of these 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 as of the date of the consolidated financial statements, as well as the reported expenses during the reporting periods. We monitor and analyze these items for changes in facts and circumstances, and material changes in these estimates could occur in the future. We base our estimates on our historical experience and on various other factors we believe to be 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. Changes in estimates are reflected in reported results for the period in which they become known. Actual results may differ materially from these estimates under different assumptions or conditions. Though the impact of the ongoing COVID-19 pandemic to our business and operating results presents additional uncertainty, we continue to use the best information available to us in our critical accounting estimates.

We discuss our accounting policies and assumptions that involve a higher degree of judgment and complexity within Note 2 to our audited consolidated financial statements appearing elsewhere in this Annual Report. We believe that our accounting policies related to research and development expense accruals involve the most significant estimation and judgment in accounting for our reported consolidated financial results.

Research and Development Expense Accruals

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued expenses. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date in our consolidated financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. Examples of estimated accrued research and development expenses include fees paid to investigative sites and CROs in connection with clinical trials; service providers in connection with preclinical development activities; and service providers related to product manufacturing, development and distribution of clinical supplies.

We currently rely on third parties for the clinical development of our product candidates and the manufacture of our product candidates to support our ongoing and future clinical trials. We pay these third parties, including consultants, CROs, CDMOs and other service providers, pursuant to contractual arrangements, which may include provisions for time and materials-based payments, project-based fees and milestone payments. We base our accrual for these expenses on our estimates of the services received and efforts expended pursuant to our contractual arrangements. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our service providers will exceed the level of services provided and result in a prepayment of the clinical expense. Payments under some of these contracts depend on factors such as the successful enrollment of patients and the completion of clinical milestones. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust our accrual or prepaid expenses accordingly.

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

Results of Operations

Comparison of the Years Ended December 31, 2021 and 2020

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

	Years Ended December 31,		Increase /
	2021	2020	(Decrease)
License and collaboration agreement revenues	$ —	$ 10,455	$ (10,455)
Research and development expenses	23,264	17,291	5,973
General and administrative expenses	10,751	9,075	1,676
Other income (expense), net	238	(319)	557

License and collaboration agreement revenues. Revenues of $10.5 million for the year ended December 31, 2020 consisted primarily of $10.0 million from license and collaboration agreement earned under the Kyorin Agreement.

Research and development expenses. Research and development expenses were $23.3 million and $17.3 million for the years ended December 31, 2021 and 2020, respectively. The increase of $6.0 million was due primarily to an increase of $6.2 million in product development and manufacturing costs for efzofitimod and ATYR2810, an increase of $1.8 million research development for efzofitimod, ATYR2810 and our discovery programs and an increase of $1.1 million in compensation related expenses. The increase was offset by a decrease of $3.1 million in clinical trial expenses due to the completion of the Phase 1b/2a sarcoidosis clinical trial in September 2021 and the COVID-19 clinical trial in December 2020.

General and administrative expenses. General and administrative expenses were $10.8 million and $9.1 million for the years ended December 31, 2021 and 2020, respectively. The increase of $1.7 million was due primarily to a $1.2 million increase in compensation related expenses, a $0.2 million increase in insurance costs, a $0.2 million increase in professional fees and $0.1 million increase in taxes and licenses.

Other income (expense), net. Other income (expense) was $0.2 million and $(0.3) million for years ended December 31, 2021 and 2020, respectively. The change was primarily a result of a reduction in interest expense due to the repayment of our term loans in November 2020.

Recent Accounting Pronouncements

For discussion of recently issued accounting pronouncements, refer to the Section titled “Recent Accounting Pronouncements” within Note 2 of our consolidated financial statements included in this Annual Report.

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

Not Applicable.

Item 8. Financial Statements and Supplementary Data.

Report of Independent Registered Public Accounting Firm

The Stockholders and Board of Directors of aTyr Pharma, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of aTyr Pharma, Inc. (the Company) as of December 31, 2021 and 2020, the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2021, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2021 and 2020, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2021, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

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

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

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

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of the critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Accrued clinical studies costs	
Description of the Matter	During 2021, the Company incurred $23.3 million for research and development expenses and as of December 31, 2021 recorded an accrual for $1.0 million of clinical studies costs. A substantial portion of the Company's ongoing research and development activities are conducted by third-party service providers, including clinical research organizations and contracted development and manufacturing organizations. As described in Note 2 to the consolidated financial statements, external costs for clinical studies to be paid are accrued and expensed based upon work completed in accordance with contractual arrangements. Auditing management's accounting for accrued clinical studies costs is especially challenging because it is dependent on data from third parties and involves judgments applied by management to determine the commencement and completion date of vendor tasks as well as the extent of work performed during the reporting period, which may not match the pattern of bills received or payments made to third-party service providers. The testing of accrued clinical studies costs is dependent upon a high-volume of data and input exchanged between clinical personnel and third-party service providers, which includes the total trial management costs, number of sites activated, number of patients enrolled, and number of patient visits, which is tracked in spreadsheets and other end user computing programs.
How We Addressed the Matter in Our Audit	Our substantive testing procedures over the completeness of the Company's accrued clinical studies costs include obtaining from third-parties confirmation of total costs billed and work completed as of December 31, 2021 for significant clinical trials. We obtained an understanding of the status of significant clinical trial activities from accounting personnel and the clinical project managers to understand the status of significant clinical trial activities. To assess the appropriate measurement of accrued clinical studies costs, we inspected key terms, timelines of completion, activities and costs for a sample of vendor contracts, including amendments, and compared these to management's analyses used in tracking the progress of service agreements. We also inspected a sample of subsequent payments, obtained invoice support and tested the expense was recorded to the appropriate period.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2008.

San Diego, California

March 15, 2022

aTyr Pharma, Inc.
Consolidated Balance Sheets
(in thousands, except share and per share data)

	December 31, 2021	December 31, 2020
Assets		
Current assets:		
Cash and cash equivalents	$ 2,336	$ 16,952
Available-for-sale investments	105,575	14,737
Other receivables	435	2,039
Prepaid expenses	5,223	1,803
Total current assets	113,569	35,531
Property and equipment, net	543	899
Right-of-use assets	1,267	2,083
Other assets	158	213
Total assets	$ 115,537	$ 38,726
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 1,031	$ 1,431
Accrued expenses	4,002	3,572
Current portion of operating lease liability	980	861
Total current liabilities	6,013	5,864
Long-term operating lease liability, net of current portion	398	1,378
Commitments and contingencies (Note 6)		
Stockholders' equity:		
Preferred stock, $0.001 par value per share; 5,000,000 undesignated authorized shares; Class X Convertible Preferred Stock issued and outstanding shares – 0 as of December 31, 2021 and 2020, respectively	—	—
Common stock, $0.001 par value per share; 42,500,000 and 21,425,000 authorized shares as of December 31, 2021 and 2020, respectively; issued and outstanding shares – 27,793,035 and 11,018,954 as of December 31, 2021 and 2020, respectively	28	11
Additional paid-in capital	481,832	370,210
Accumulated other comprehensive loss	(263)	(43)
Accumulated deficit	(372,296)	(338,528)
Total aTyr Pharma stockholders' equity	109,301	31,650
Noncontrolling interest in Pangu BioPharma Limited	(175)	(166)
Total stockholders' equity	109,126	31,484
Total liabilities and stockholders' equity	$ 115,537	$ 38,726

See accompanying notes.

aTyr Pharma, Inc.
Consolidated Statements of Operations
(in thousands, except share and per share data)

	Years Ended December 31,		
	2021	**2020**	**2019**
Revenues:			
License and collaboration agreement revenues	$ —	$ 10,455	$ 422
Total revenues	—	10,455	422
Operating expenses:			
Research and development	23,264	17,291	14,048
General and administrative	10,751	9,075	9,352
Total operating expenses	34,015	26,366	23,400
Loss from operations	(34,015)	(15,911)	(22,978)
Total other income (expense), net	238	(319)	(785)
Consolidated net loss	(33,777)	(16,230)	(23,763)
Net loss attributable to noncontrolling interest in Pangu BioPharma Limited	9	6	160
Net loss attributable to aTyr Pharma, Inc.	$ (33,768)	$ (16,224)	$ (23,603)
Net loss per share, basic and diluted	$ (1.77)	$ (1.77)	$ (7.03)
Shares used in computing net loss per share, basic and diluted	19,080,878	9,160,269	3,355,600

See accompanying notes.

aTyr Pharma, Inc.
Consolidated Statements of Comprehensive Loss
(in thousands)

	Years Ended December 31,		
	2021	**2020**	**2019**
Consolidated net loss	$ (33,777)	$ (16,230)	$ (23,763)
Other comprehensive loss:			
Change in unrealized gain (loss) on available-for-sale investments, net of tax	(220)	(3)	20
Comprehensive loss	(33,997)	(16,233)	(23,743)
Comprehensive loss attributable to noncontrolling interest in Pangu BioPharma Limited	9	6	160
Comprehensive loss attributable to aTyr Pharma, Inc. common stockholders	$ (33,988)	$ (16,227)	$ (23,583)

See accompanying notes.

aTyr Pharma, Inc.
Consolidated Statements of Stockholders' Equity
(in thousands, except share data)

	Convertible Preferred Stock		Common Stock		Additional Paid-In	Other Comprehensive	Accumulated	Noncontrolling	Total Stockholders'
	Shares	Amount	Shares	Amount	Capital	Gain/(Loss)	Deficit	Interest	Equity
Balance as of December 31, 2018	2,285,952	$ 2	2,186,389	$ 2	$ 332,407	$ (60)	$ (298,701)	$ —	$ 33,650
Conversion of preferred stock to common stock	(641,991)	—	229,283	—	—	—	—	—	—
Issuance of common stock upon release of restricted stock units	—	—	7,487	—	—	—	—	—	—
Issuance of common stock pursuant to employee stock purchase plan	—	—	3,117	—	13	—	—	—	13
Issuance of common stock from at-the-market offerings, net of offering costs	—	—	805,357	1	4,404	—	—	—	4,405
Issuance of common stock from registered direct offering, net of offering costs	—	—	660,154	1	4,917	—	—	—	4,918
Stock-based compensation	—	—	—	—	1,783	—	—	—	1,783
Net unrealized gain on investments, net of tax	—	—	—	—	—	20	—	—	20
Net loss	—	—	—	—	—	—	(23,603)	(160)	(23,763)
Balance as of December 31, 2019	1,643,961	2	3,891,787	4	343,524	(40)	(322,304)	(160)	21,026
Conversion of preferred stock to common stock	(1,643,961)	(2)	587,444	1	1	—	—	—	—
Issuance of common stock from underwritten follow-on offering, net of offering costs	—	—	4,870,588	4	18,775	—	—	—	18,779
Issuance of common stock from at-the-market offerings, net of offering costs	—	—	1,657,075	2	6,435	—	—	—	6,437
Issuance of common stock upon release of restricted stock units	—	—	8,678	—	—	—	—	—	—
Issuance of common stock pursuant to employee stock purchase plan	—	—	3,382	—	10	—	—	—	10
Stock-based compensation	—	—	—	—	1,465	—	—	—	1,465
Net unrealized loss on investments, net of tax	—	—	—	—	—	(3)	—	—	(3)
Net loss	—	—	—	—	—	—	(16,224)	(6)	(16,230)
Balance as of December 31, 2020	—	—	11,018,954	11	370,210	(43)	(338,528)	(166)	31,484
Issuance of common stock upon release of restricted stock units	—	—	4,177	—	—	—	—	—	—
Issuance of	—	—	10,751	—	62	—	—	—	62

common stock upon exercise of stock options									
Issuance of common stock pursuant to employee stock purchase plan	—	—	3,382	—	11	—	—	—	11
Issuance of common stock from at-the-market offerings, net of offering costs	—	—	2,974,521	3	14,067	—	—	—	14,070
Issuance of common stock from committed purchase agreement, net of offering costs	—	—	3,000,000	3	15,233	—	—	—	15,236
Issuance of common stock from underwritten follow-on offering, net of offering costs	—	—	10,781,250	11	80,635	—	—	—	80,646
Stock-based compensation	—	—	—	—	1,614	—	—	—	1,614
Net unrealized loss on investments, net of tax	—	—	—	—	—	(220)	—	—	(220)
Net loss	—	—	—	—	—	—	(33,768)	(9)	(33,777)
Balance as of December 31, 2021	—	$ —	27,793,035	$ 28	$ 481,832	$ (263)	$ (372,296)	$ (175)	$ 109,126

See accompanying notes.

aTyr Pharma, Inc.
Consolidated Statements of Cash Flows
(in thousands)

	Years Ended December 31,		
	2021	**2020**	**2019**
Cash flows from operating activities:			
Consolidated net loss	$ (33,777)	$ (16,230)	$ (23,763)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	475	569	635
Stock-based compensation	1,614	1,465	1,783
Debt discount accretion and non-cash interest expense	—	346	707
Amortization (accretion) of premium (discount) of available-for-sale investment securities	366	110	(284)
Amortization of right-of-use assets	829	697	731
Loss (gain) on disposal of property and equipment	6	3	(28)
Changes in operating assets and liabilities:			
Other receivables	1,604	(1,939)	58
Prepaid expenses and other assets	(3,378)	(1,122)	276
Accounts payable and accrued expenses	47	1,763	162
Contract liability	—	(208)	208
Operating lease liability	(861)	(755)	(498)
Net cash used in operating activities	(33,075)	(15,301)	(20,013)
Cash flows from investing activities:			
Purchases of property and equipment	(192)	(202)	(79)
Purchases of available-for-sale investment securities	(126,506)	(21,066)	(40,647)
Maturities of available-for-sale investment securities	35,082	28,150	45,600
Proceeds from sale of property and equipment	50	18	51
Net cash (used in) provided by investing activities	(91,566)	6,900	4,925
Cash flows from financing activities:			
Proceeds from issuance of common stock through option exercises	62	—	—
Proceeds from issuance of common stock through employee stock purchase plan	11	10	13
Proceeds from issuance of common stock from at-the-market offerings, net of offering costs	14,070	6,437	4,405
Proceeds from issuance of common stock from committed purchase agreement, net of offering costs	15,236	—	—
Proceeds from issuance of common stock from underwritten follow-on offering, net of offering costs	80,646	18,779	—
Proceeds from issuance of common stock through registered direct offering, net of offering costs	—	—	4,918
Repayments on borrowings	—	(9,083)	(8,000)
Net cash provided by financing activities	110,025	16,143	1,336
Net change in cash and cash equivalents	(14,616)	7,742	(13,752)
Cash and cash equivalents at beginning of period	16,952	9,210	22,962
Cash and cash equivalents at the end of period	$ 2,336	$ 16,952	$ 9,210
Supplemental disclosure of cash flow information:			
Interest paid	$ —	$ 308	$ 1,122
Purchase of fixed assets included in accounts payable	$ —	$ 17	$ —

See accompanying notes.

1. Organization, Business and Basis of Presentation

Organization and Business

We were incorporated in the state of Delaware on September 8, 2005. We are focused on the discovery and development of innovative medicines based on novel immunological pathways.

Principles of Consolidation

Our consolidated financial statements include our accounts and our 98% majority-owned subsidiary in Hong Kong, Pangu BioPharma Limited (Pangu BioPharma). All intercompany transactions and balances are eliminated in consolidation.

Liquidity and Financial Condition

We have incurred losses and negative cash flows from operations since our inception. As of December 31, 2021, we had an accumulated deficit of $372.3 million and we expect to continue to incur net losses for the foreseeable future. As of December 31, 2021, our cash, cash equivalents and available-for-sale investments were $107.9 million. We believe that our current cash, cash equivalents and available-for-sale investments, will be sufficient to meet our anticipated cash requirements for a period of at least one year from the date of this Annual Report.

We do not expect to generate any revenues from product sales unless and until we successfully complete development and obtain regulatory approval for one or more of our product candidates, which we expect will take a number of years at a minimum. If we obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. Accordingly, we will need to raise substantial additional capital to fund our operations. The amount and timing of our future funding requirements will depend on many factors, including the pace and results of our preclinical and clinical development efforts and the timing and nature of the regulatory approval process for our product candidates. We anticipate that we will seek to fund our operations through equity offerings, grant funding, collaborations, strategic partnerships and/or licensing arrangements, and when we are closer to commercialization of our product candidates potentially through debt financings. However, we may be unable to raise additional capital or enter into such arrangements when needed on favorable terms or at all. Our failure to raise capital or enter into such arrangements when needed would have a negative impact on our financial condition and ability to develop our product candidates.

Use of Estimates

Our consolidated financial statements are prepared in accordance with generally accepted accounting principles (GAAP). The preparation of our consolidated financial statements requires us to make estimates and assumptions that impact the reported amounts of assets, liabilities and expenses and the disclosure for these items in our consolidated financial statements and accompanying notes. The most significant estimates in our consolidated financial statements relate to the fair value of equity issuances and awards, and clinical trial and research and development expenses. Although these estimates are based on our knowledge of current events and actions we may undertake in the future, actual results may ultimately differ materially from these estimates and assumptions.

Segment Reporting

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 in making decisions regarding resource allocation and assessing performance. We view our operations and manage our business in one operating segment.

2. Summary of Significant Accounting Policies

Cash and Cash Equivalents

Cash and cash equivalents consist primarily of readily available checking, money market accounts and money market funds. We consider all highly liquid investments that mature in three months or less when purchased to be cash equivalents.

Investment Securities

Investment securities primarily consist of investment grade corporate debt securities, municipal bond securities and commercial paper. We classify all investment securities as available-for-sale. Investment securities are carried at fair value, with the unrealized gains and losses, if any, reported as a component of other comprehensive income (loss) in stockholders' equity until realized. Realized gains and losses from the sale of investment securities, if any, are determined on a specific identification basis. A decline in the market

value of any investment security below cost that is determined to be other than temporary will result in an impairment charge to earnings and a new cost basis for the security is established. No such impairment charges were recorded for any period presented. Premiums and discounts are amortized or accreted over the life of the related security as an adjustment to yield using the straight-line method and are included in interest income. Interest income is recognized when earned. As of December 31, 2021, we held an aggregate total of $105.6 million of investment securities which consisted of corporate debt securities, municipal bonds, and commercial paper all of which will mature in less than two years, and there was an unrealized loss of approximately $0.2 million between the amortized cost and fair value of these investment securities. As of December 31, 2020, we held $14.7 million of corporate debt securities, asset-backed securities and commercial paper, all of which mature in less than one year, and there was an unrealized loss of approximately $3,000 between the amortized cost and fair value of these investment securities.

Concentration of Credit Risk

Financial instruments that potentially subject us to significant concentration of credit risk consist primarily of cash, cash equivalents and investment securities. We have established guidelines regarding diversification of investments and their maturities, which are designed to maintain principal and maximize liquidity. We maintain deposits in federally insured financial institutions in excess of federally insured limits. We have not experienced any losses in such accounts and we believe that we are not exposed to significant credit risk due to the financial position of the depository institutions in which those deposits are held.

Property and Equipment

Property and equipment are stated at cost and depreciated on a straight-line basis over the estimated useful life of the related assets (generally three to seven years). Leasehold improvements are stated at cost and amortized on a straight-line basis over the lesser of the remaining term of the related lease or the estimated useful life of the leasehold improvements. Repairs and maintenance costs are charged to expense as incurred.

Impairment of Long-Lived Assets

Long-lived assets consist primarily of property and equipment. An impairment loss is recorded if and when events and circumstances indicate that assets might be impaired and the undiscounted cash flows estimated to be generated by those assets are less than the carrying amount of those assets. While our current and historical operating losses are indicators of impairment, we believe that future cash flows to be received support the carrying value of our long-lived assets and, accordingly, have not recognized any impairment losses since inception.

Accrued Expenses

Accrued expenses include salaries, wages, benefits costs, consulting fees, legal and research and development costs. Accrued clinical studies costs of $1.0 million and $1.1 million as of December 31, 2021 and 2020, respectively, included clinical studies and product manufacturing costs. We have entered into contractual arrangements related to our clinical studies with clinical research organizations (CROs) and contracted development and manufacturing organizations (CDMOs) and recognize expense based on work completed and efforts expended pursuant to our contractual arrangements. We make estimates of our accrued CRO costs as of each balance sheet date based on facts and circumstances known at the time and include total trial management costs, sites activated, patients enrolled and number of patient visits. We estimate the time period over which services will be performed and the level of effort to be expended in each period. There may be instances in which payments made to our service providers including CROs and CDMOs, will temporarily exceed the level of services provided and result in a prepayment of the expense. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid expense balance accordingly. Historically, our estimated accrued liabilities have materially approximated actual expenses incurred.

Leases

We determine if an arrangement is a lease at inception. Short-term leases with an initial term of 12 months or less are not recorded on the balance sheet. For long-term operating leases with an initial term of greater than 12 months, we recognized an operating right-of-use asset (ROU) and a lease liability based on the present value of future lease payments using an estimated rate of interest that we would pay to borrow equivalent funds on a collateralized basis at the lease commencement date. We determine the lease term at the commencement date by considering whether renewal options and termination options are reasonably assured of exercise. Rent expense for the operating lease is recognized on a straight-line basis over the lease term and is included in operating expenses in our consolidated statements of operations.

If a lease is modified, the modified contract is evaluated to determine whether it is or contains a lease. If a lease continues to exist, the lease modification is determined to be a separate contract when the modification grants the lessee an additional ROU that is not included in the original lease and the lease payments increase commensurate with the standalone price for the additional ROU. A lease modification that results in a separate contract will be accounted for in the same manner as a new lease. For a modification that is not a separate contract, we reassess the lease classification using the modified terms and conditions and the facts and circumstances

as of the effective date of the modification and recognize the amount of the remeasurement of the lease liability for the modified lease as an adjustment to the corresponding operating lease ROU asset.

Our right-of-use assets consist of an operating lease for our facility headquarters. We have a noncancelable operating lease that includes certain tenant improvement allowances and is subject to base lease payments, which escalate over the term of the lease, additional charges for common area maintenance and other costs. We currently do not have any finance leases.

We do not separate lease and non-lease components for our long-term leases.

Rent expense for the operating lease is recognized on a straight-line basis over the lease term and is included in our consolidated statement of operations. Variable lease payments, including lease operating expenses, are recorded as incurred.

Revenue Recognition

We evaluate our agreements under ASC Topic 606, *Revenue from Contracts with Customers* and ASC Topic 808, *Collaborative Arrangements*. We recognize revenue when we transfer promised goods or services to customers in an amount that reflects the consideration to which we expect to be entitled in exchange for those goods or services. In determining the appropriate amount of revenue to be recognized as we fulfill our obligations under our agreement, we perform the following steps: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance obligations including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraint on variable consideration; (iv) allocation of the transaction price to the performance obligations; and (v) recognition of revenue when (or as) we satisfy each performance obligation. As part of the accounting for these arrangements, we must develop assumptions that require judgment to determine the stand-alone selling price for each performance obligation identified in the contract. We use key assumptions to determine the stand-alone selling price, which may include forecasted revenues, development timelines, reimbursement rates for personnel costs, discount rates and probabilities of technical and regulatory success.

We recognize revenue in one of two ways, over time or at a point in time. We recognize revenue over time when we are executing on our performance obligation over time and our partner receives benefit over time. For example, we recognize revenue over time when we provide research and development services. We recognize revenue at a point in time when we transfer control of a distinct performance obligation to our partner. For example, if a license to our intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, we recognize revenues from non-refundable, up-front fees allocated to the license when the license is transferred to the licensee and the licensee is able to use and benefit from the license.

Research and Development Costs

Research and development costs are expensed as incurred. Research and development costs include: salaries and employee-related expenses, including stock-based compensation and benefits for personnel in research and product development functions; costs associated with conducting our preclinical, development and regulatory activities, including fees paid to third-party professional consultants, service providers and our scientific, therapeutic and clinical advisors; costs to acquire, develop and manufacture preclinical study and clinical trial materials; costs incurred under clinical trial agreements with clinical research organizations and investigative sites; costs for laboratory supplies; payments related to licensed products and technologies; allocated facilities and information technology costs; and depreciation.

Patent Costs

Costs related to filing and pursuing patent applications are recorded as general and administrative expense and expensed as incurred since recoverability of such expenditures is uncertain.

Stock-Based Compensation

Stock-based compensation expense represents the grant date fair value of employee stock option grants recognized as expense over the requisite service period of the awards (usually the vesting period) on a straight-line basis. We estimate fair value of stock option grants using the Black-Scholes option pricing model. We estimate the fair value using assumptions, including the risk-free interest rate, the expected volatility of a peer group of similar companies, the expected term of the awards and the expected dividend yield. These estimates involve inherent uncertainties and the application of management's judgment. If factors change and different assumptions are used, our stock-based compensation expense could be materially different in the future. We follow ASC Topic 718, *Compensation – Stock Compensation* as guidance for accounting modification.

Income Taxes

We account for income taxes under the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements. Under this method, deferred tax assets and liabilities are determined on the basis of the differences between the financial statements and tax basis of assets

and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. The effect of a change in tax rates on deferred tax assets and liabilities is recognized as income in the period that includes the enactment date.

We recognize net deferred tax assets to the extent that we believe these assets are more likely than not to be realized. In making such a determination, we consider all available positive and negative evidence, including future reversals of existing taxable temporary differences, projected future taxable income, tax-planning strategies and results of recent operations. If we determine that we would be able to realize the deferred tax assets in the future in excess of their net recorded amount, we would make an adjustment to the deferred tax asset valuation allowance, which would reduce the provision for income taxes.

We record uncertain tax positions on the basis of a two-step process whereby (1) we determine whether it is more likely than not that the tax positions will be sustained on the basis of the technical merits of the position and (2) for those tax positions that meet the more-likely-than-not recognition threshold, we recognize the largest amount of tax benefit that is more than 50% likely to be realized upon ultimate settlement with the related tax authority. We recognize interest and penalties related to unrecognized tax benefits within income tax expense. Any accrued interest and penalties are included within the related tax liability.

Net Loss Per Share

Basic net loss per share is calculated by dividing the net loss attributable to common stockholders by the weighted average number of common shares outstanding for the period, without consideration for common stock equivalents. Diluted 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 common stock and common stock equivalents outstanding for the period determined using the treasury-stock method. Dilutive common stock equivalents are comprised of convertible preferred stock, warrants for common stock, options and restricted stock units outstanding under our stock option plan and estimated shares to be purchased under our employee stock purchase plan. For all periods presented, there is no difference in the number of shares used to calculate basic and diluted shares outstanding due to our net loss position.

Potentially dilutive securities not included in the calculation of diluted net loss per share because to do so would be anti-dilutive are as follows (in common share equivalents):

	Years Ended December 31,		
	2021	2020	2019
Class X preferred stock (if-converted to common stock)	—	—	587,445
Common stock warrants	13,760	13,904	13,904
Common stock options and restricted stock units	1,420,050	584,211	363,553
Employee stock purchase plan	2,045	1,602	1,958
Total	1,435,855	599,717	966,860

The following table summarizes our net loss per share (in thousands, except per share data):

	Years Ended December 31,		
	2021	2020	2019
Numerator:			
Net loss attributable to aTyr Pharma, Inc.	$ (33,768)	$ (16,224)	$ (23,603)
Denominator:			
Shares used in computing net loss per share, basic and diluted	19,080,878	9,160,269	3,355,600
Net loss per share - basic and diluted	$ (1.77)	$ (1.77)	$ (7.03)

Recent Accounting Pronouncements

In June 2016, the Financial Accounting Standards Board (FASB) issued Accounting Standards Update (ASU) No. 2016-13, *Financial Instruments – Credit Losses* (Topic 326), to provide financial statement users with more decision-useful information about the expected credit losses on financial instruments and other commitments to extend credit held by a reporting entity at each reporting date. To achieve this objective, the amendments in Topic 326 replace the incurred loss impairment methodology in current GAAP with a methodology that reflects expected credit losses and requires consideration of a broader range of reasonable and supportable information to inform credit loss estimates. Topic 326 is effective for fiscal years beginning after December 15, 2022, including interim periods within those fiscal years for smaller reporting companies. We expect the adoption of the amendments in Topic 326 to have an immaterial effect on our consolidated financial position or the results of its operations when such amendment is adopted.

In December 2019, the FASB issued ASU No. 2019-12, *Income Taxes* (Topic 740), *Simplifying the Accounting for Income Taxes* to identify, evaluate, and improve areas of GAAP for which costs and complexity can be reduced while maintaining or improving the usefulness of the information provided to users of financial statements. The amendments for Topic 740 simplify the accounting for income taxes by removing certain exceptions to the general principles in Topic 740. The amendments also improve consistent application of and simplify GAAP for other areas of Topic 740 by clarifying and amending existing guidance. Topic 740 is effective for fiscal years beginning after December 15, 2020 which we adopted prospectively on January 1, 2021. The adoption did not have a material effect on our consolidated financial position or results of operations.

3. Fair Value Measurements

The carrying amounts of cash equivalents, prepaid and other assets, accounts payable and accrued liabilities are considered to be representative of their respective fair values because of the short-term nature of those instruments. Investment securities are recorded at fair value.

The accounting guidance defines fair value, establishes a consistent framework for measuring fair value and expands disclosure for each major asset and liability category measured at fair value on either a recurring or nonrecurring basis. Fair value is defined as an exit price, representing the amount that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. As such, fair value is a market-based measurement that should be determined based on assumptions that market participants would use in pricing an asset or liability. As a basis for considering such assumptions, the accounting guidance establishes a three-tier fair value hierarchy, which prioritizes the inputs used in measuring fair value as follows:

Level 1: Observable inputs such as quoted prices in active markets.

Level 2: Inputs, other than the quoted prices in active markets that are observable either directly or indirectly.

Level 3: Unobservable inputs in which there is little or no market data, which require the reporting entity to develop its own assumptions.

Financial assets measured at fair value on a recurring basis consist of investment securities. Investment securities are recorded at fair value, defined as the exit price in the principal market in which we would transact, representing the amount that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. Level 2 securities are valued using quoted market prices for similar instruments, non-binding market prices that are corroborated by observable market data, or discounted cash flow techniques and include our investments in asset-backed securities, commercial paper, corporate debt securities and municipal bonds. We have no financial liabilities measured at fair value on a recurring basis. None of our non-financial assets and liabilities are recorded at fair value on a non-recurring basis. No transfers between levels have occurred during the periods presented.

Assets measured at fair value on a recurring basis are as follows (in thousands):

		Fair Value Measurements Using		
	Total	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
As of December 31, 2021				
Assets:				
Current:				
Cash equivalents	$ 2,052	$ 2,052	$ —	$ —
Available-for-sale investments:				
Commercial paper	36,921	—	36,921	—
Corporate debt securities	55,713	—	55,713	—
Municipal bonds	12,941	—	12,941	—
Total available-for-sale investments	105,575	—	105,575	—
Total assets measured at fair value	$ 107,627	$ 2,052	$ 105,575	$ —

	Fair Value Measurements Using			
	Total	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
As of December 31, 2020				
Assets:				
Current:				
Cash equivalents	$ 13,708	$ 13,708	$ —	$ —
Available-for-sale investments:				
Asset-backed securities	2,219	—	2,219	—
Commercial paper	5,494	—	5,494	—
Corporate debt securities	7,024	—	7,024	—
Total available-for-sale investments	14,737	—	14,737	—
Total assets measured at fair value	$ 28,445	$ 13,708	$ 14,737	$ —

As of December 31, 2021 and 2020, available-for-sale investments are detailed as follows (in thousands):

		December 31, 2021			
	Contractual Maturity	Gross Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Market Value
Available-for-sale investments:					
Commercial paper	Within 1 year	$ 36,956	$ —	$ (35)	$ 36,921
Corporate debt securities	1 to 2 years	55,859	—	(146)	55,713
Municipal bonds	1 to 2 years	12,973	—	(32)	12,941
		$ 105,788	$ —	$ (213)	$ 105,575

		December 31, 2020			
	Contractual Maturity	Gross Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Market Value
Available-for-sale investments:					
Asset-backed securities	Within 1 year	$ 2,218	$ 1	$ —	$ 2,219
Commercial paper	Within 1 year	5,491	3	—	5,494
Corporate debt securities	Within 1 year	7,021	3	—	7,024
		$ 14,730	$ 7	$ —	$ 14,737

At each reporting date, we perform an evaluation of impairment to determine if the unrealized losses are other-than-temporary. Factors considered in determining whether a loss is other-than-temporary include the length of time and extent to which fair value has been less than the cost basis, the financial condition of the issuer, and our intent and ability to hold the investment until recovery of its amortized cost basis. Based on our evaluation, we determined that the unrealized losses were not other-than-temporary as of December 31, 2021.

As of December 31, 2021, all available-for-sale investments were in a gross unrealized loss position and have been in such position for less than twelve months. As of December 31, 2020, available-for-sale investments were in a gross unrealized gain position.

4. License, Collaboration and Other Agreements

Kyorin Pharmaceutical Co., Ltd.

In January 2020, we entered into a collaboration and license agreement with Kyorin Pharmaceutical Co., Ltd. (Kyorin) for the development and commercialization of efzofitimod (the non-proprietary name for our lead therapeutic candidate ATYR1923) for interstitial lung diseases (ILD) in Japan. Under the agreement (the Kyorin Agreement), Kyorin received an exclusive right to develop and commercialize efzofitimod in Japan for all forms of ILD. Under the terms of the Kyorin Agreement, Kyorin is obligated to fund all research, development, regulatory, marketing and commercialization activities in Japan. In September 2020, Kyorin began dosing

patients in a Phase 1 clinical trial of efzofitimod (known as KRP-R120 in Japan) and completed the last subject visit in December 2020. The Phase 1 clinical trial, which was conducted and funded by Kyorin, is a placebo-controlled study to evaluate the safety, pharmacokinetics and immunogenicity of efzofitimod. Efzofitimod was observed to be generally well-tolerated with no drug-related serious adverse events and pharmacokinetics findings were consistent with previous studies of efzofitimod. We received an $8.0 million upfront payment in January 2020 and a $2.0 milestone payment in January 2021 upon completion of enrollment in the Phase 1 clinical trial in December 2020, and we are eligible to receive up to an additional $165.0 million in the aggregate upon achievement of certain development, regulatory and sales milestones, as well as tiered royalties ranging from the mid-single digits to mid-teens on net sales in Japan.

Either party may terminate the Kyorin Agreement in the event that the other party breaches the agreement and fails to cure the breach, becomes insolvent or challenges certain of the intellectual property rights licensed under the agreement.

We assessed our license and collaboration with Kyorin in accordance with Topic 606 and concluded that Kyorin is a customer. We identified the following performance obligations under the Kyorin Agreement: 1) the license of efzofitimod for ILD in Japan; and 2) free clinical trial material for Kyorin's Phase 1 clinical trial. The $8.0 million upfront payment received from Kyorin is non-refundable and non-creditable and is considered fixed consideration. We determined that the relative stand-alone selling price was $7.9 million when the license was delivered to Kyorin in January 2020. We determined that the relative standalone selling price was $0.1 million for the free clinical trial material delivered to Kyorin in June 2020, using the "expected cost plus a margin" approach. In December 2020, Kyorin completed the last subject visit in its Phase 1 trial of efzofitimod. This achievement triggered a $2.0 million milestone payment, which we received in January 2021.

The remaining milestones and royalty payments under the Kyorin Agreement are variable consideration. Since the milestone payments are binary in nature, we will use the "most-likely" method to evaluate whether the milestones should be included as revenue. We will constrain these amounts until the milestone is probable of being achieved. The royalties are dependent on future sales by Kyorin which are at the full discretion of Kyorin. Accordingly, we will apply a constraint to these amounts until the future sale sales have occurred.

Hong Kong University of Science and Technology

In March 2020, our subsidiary, Pangu BioPharma, together with the Hong Kong University of Science and Technology (HKUST) was awarded a grant of approximately $750,000 to build a high-throughput platform for the development of bi-specific antibodies. The project is being funded by the Hong Kong Government's Innovation and Technology Commission (ITC) under the Partnership Research Program (PRP). The PRP aims to support research and development projects undertaken by companies in collaboration with local universities and public research institutions. The ITC funded approximately 50% of the total estimated project cost, with aTyr contributing the remaining 50%. The research grant agreement between Pangu BioPharma, HKUST and the Government of the Hong Kong Special Administration Region was effective April 1, 2020. The term of the project was initially for two years and in December 2021, due to the ongoing COVID-19 pandemic, was extended for an additional six months with no additional cost.

All the contributions provided by the ITC are paid to HKUST and we record expenses incurred related to this grant award when incurred. Expenses for the years ended December 31, 2021 and 2020 were $0.4 million and $0.2 million, respectively.

5. Balance Sheet Details

Prepaid expenses consist of the following (in thousands):

	December 31,	
	2021	**2020**
Prepaid clinical and research expense	$ 557	$ 583
Prepaid manufacturing expenses (1)	4,188	513
Other prepaid expenses	478	707
	$ 5,223	$ 1,803

(1) Prepaid manufacturing expenses of $3.7 million incurred in 2021 included a reservation fee and raw materials for manufacturing of efzofitimod clinical trial materials planned to occur in the second half of 2022.

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

	December 31,	
	2021	2020
Computer and office equipment	$ 616	$ 552
Scientific and laboratory equipment	4,383	5,270
Tenant improvements	1,701	1,701
	6,700	7,523
Less accumulated depreciation and amortization	(6,157)	(6,624)
	$ 543	$ 899

As of December 31, 2021, 2020 and 2019, depreciation expense was $0.5 million, $0.6 million and $0.6 million, respectively.

Accrued expenses consist of the following (in thousands):

	December 31,	
	2021	2020
Accrued salaries, wages and benefits	$ 2,326	$ 1,809
Accrued clinical studies costs	$ 1,004	$ 1,089
Other accrued expenses	672	674
	$ 4,002	$ 3,572

6. Commitments and Contingencies

Facility Lease

We have a non-cancelable facility lease that is subject to base lease payments, which escalate over the term of the lease, additional charges for common area maintenance and other costs. In July 2018, we entered into a lease amendment that reduced the space we lease from 24,494 square feet to 20,508 square feet and extended the lease term to May 2023. With the lease amendment, we do not have an option to extend the lease.

Operating lease expense for each of the years ended December 31, 2021, 2020 and 2019 was $1.0 million. As of December 31, 2021 and 2020, the weighted average remaining lease term was 1.4 years and 2.4 years, respectively, and the weighted average discount rate for each year was 9.6%.

Future minimum payments under the non-cancelable facility lease and reconciliation to the operating lease liability as of December 31, 2021 were as follows (in thousands):

	Operating Lease
2022	$ 1,062
2023	404
Less: Amount representing interest	(88)
Present value of lease payments	1,378
Less: Current portion of operating lease liability	(980)
Long-term operating lease liability, net of current portion	$ 398

7. Stockholders' Equity

Underwritten Follow-On Public Offerings

In September 2021, we completed an underwritten follow-on public offering of 10,781,250 shares of our common stock, including the full exercise of the underwriters' option to purchase additional shares, at a price to the public of $8.00 per share. The total net proceeds from the offering were approximately $80.6 million, after deducting underwriting discounts, commissions and offering expenses payable by us.

In February 2020, we completed an underwritten follow-on public offering of 4,235,294 shares of our common stock at a price to the public of $4.25 per share. In March 2020, the underwriters fully exercised their over-allotment option for the issuance of an additional 635,294 shares of common stock. The total net proceeds from the offering were approximately $18.8 million, after deducting underwriting discounts, commissions and offering expenses payable by us.

At-the-Market Offering Program

In March 2021, we entered into a Capital on Demand™ Sales Agreement with JonesTrading Institutional Services LLC (JonesTrading) for an at-the-market offering (ATM Offering Program), pursuant to which we can sell from time to time, at our option, up to an aggregate of $25.0 million of shares of our common stock through JonesTrading, as sales agent or principal. JonesTrading is entitled to a commission at a fixed rate equal of up to 3% of the gross proceeds. For the year ended December 31, 2021, we sold an aggregate of 986,267 shares of common stock at an average price of $4.75 per share for net proceeds of $4.4 million under the JonesTrading ATM Offering Program.

In May 2019, we entered into a sales agreement with H.C. Wainwright & Co., LLC (Wainwright) with respect to an ATM Offering Program under which we could offer and sell shares of our common stock having an aggregate offering price of up to $10.0 million. Wainwright was entitled to a commission at a fixed rate equal to 3% of the gross proceeds. In November 2020, we amended our sales agreement with Wainwright to increase the amount of the ATM Offering Program up to $20.0 million. In March 2021, the ATM Offering Program with Wainwright automatically terminated upon the issuance and sale of all of the shares of common stock having an aggregate offering price of $20.0 million. Under the ATM Offering Program with Wainwright, during 2020, we sold an aggregate of 1,657,075 shares of common stock at an average price of $4.07 per share for net proceeds of $6.4 million. Prior to the termination of the sales agreement with Wainwright, in 2021, we sold an aggregate of 1,988,254 shares of common stock at an average price of $4.99 per share for net proceeds of $9.6 million under the Wainwright ATM Offering Program.

Purchase Agreement

In September 2020, we entered into a common stock purchase agreement (Purchase Agreement) with Aspire Capital Fund, LLC (Aspire Capital), which provides that, upon the terms and subject to the conditions and limitations set forth therein, Aspire Capital is committed to purchase up to an aggregate of $20.0 million of shares of our common stock at our request from time to time during the 30 month term of the Purchase Agreement. Concurrently with entering into the Purchase Agreement, we also entered into a registration rights agreement with Aspire Capital, in which we agreed to file one or more registration statements, as permissible and necessary to register under the Securities Act of 1933, as amended, for the resale of the shares of our common stock that have been and may be issued to Aspire Capital under the Purchase Agreement. For the year ended December 31, 2021, we sold an aggregate of 3,000,000 shares of common stock at an average price of $5.09 per share for net proceeds of $15.2 million under this Purchase Agreement. We did not sell any shares of common stock to Aspire Capital under this Purchase Agreement for the year ended December 31, 2020.

2014 Stock Plan

We adopted a stock option plan in 2007 (the 2007 Plan), which was subsequently amended, restated and renamed in July 2014 (the 2014 Plan) to provide for the incentive stock options, nonstatutory stock options, stock and rights to purchase restricted stock to eligible recipients. Recipients of incentive stock options are eligible to purchase shares of our common stock at an exercise price equal to no less than the estimated fair market value of such stock on the date of grant. The maximum term of options under the 2014 Plan is ten years. Options granted generally vest over four years. Shares underlying any awards under the 2014 Plan that are forfeited, canceled, reacquired by us prior to vesting, satisfied without the issuance of stock or otherwise terminated (other than by exercise) will be added to shares available for issuance under the 2015 Plan.

2015 Stock Plan

In April 2015, our board of directors adopted, and our stockholders approved, the 2015 Stock Plan (the 2015 Plan). The 2015 Plan became effective on May 6, 2015 and we ceased granting any new awards under our 2014 Plan. Awards granted under the 2014 Plan prior to our IPO that are forfeited, canceled, reacquired by us prior to vesting satisfied without the issuance of stock or otherwise terminated (other than by exercise) will be added to shares available for issuance under the 2015 Plan. At our 2020 Annual Meeting of Stockholders and at our 2021 Annual Meeting of Stockholders, our stockholders approved an amendment to increase the number of shares of common stock reserved under the 2015 Plan by 350,000 shares and 750,000 shares, respectively. Total shares available for issuance under the 2015 Plan as of December 31, 2021 were 420,896. Shares underlying any awards under the 2015 Plan that are forfeited, canceled, reacquired by us prior to vesting, satisfied without the issuance of stock or otherwise terminated (other than by exercise) will be added to shares available for issuance under the 2015 Plan.

The maximum term of options granted under 2015 Plan is ten years. For an initial grant to an employee, 25% of the options generally vest on the first anniversary of the original vesting date, with the balance vesting monthly over the remaining three years. For subsequent grants to an employee, the options generally vest monthly over a four-year term.

Inducement Grants

Options under inducement grants vest over a period of four years, with 25% vesting on the one year anniversary of the grant date and the remaining 75% vesting on a monthly basis over three years thereafter, subject to continuous employment. These options were inducement grants issued outside of the 2015 Plan in accordance with Nasdaq Listing Rule 5635(c)(4). In addition, from time to time, we may make inducement grants of stock options to new employees.

In October 2021, we granted a non-qualified option to purchase 70,000 shares of our common stock at an exercise price of $8.73 per share as an inducement award in connection with the hiring of our Vice President, Regulatory Affairs, and in December 2021, we granted a non-qualified option to purchase 70,000 shares of our common stock at an exercise price of $7.77 per share as an inducement award in connection with the hiring of our Vice President, Human Resources.

We intend to file a registration statement on Form S-8 to register the shares of common stock underlying the options granted under the inducement grants prior to the time at which this option becomes exercisable.

Employee Stock Purchase Plan

In April 2015, our board of directors adopted, and our stockholders approved, our 2015 Employee Stock Purchase Plan (the 2015 ESPP). The 2015 ESPP became effective on May 6, 2015. As of December 31, 2021, total shares reserved for issuance under the 2015 ESPP were 71,933.

Stock-based Compensation

Stock Options

Stock option activity is summarized as follows:

	Number of Outstanding Stock Options	Weighted Average Exercise Price	Weighted Remaining Contractual Term	Aggregate Intrinsic Value
Outstanding as of December 31, 2020	576,534	$ 23.33		
Granted	892,239	$ 5.08		
Exercises	(10,751)	$ 5.78		
Canceled/forfeited/expired	(45,472)	$ 22.38		
Outstanding as of December 31, 2021	1,412,550	$ 12.01	8.46	$ 3,134,377
Options vested and expected to vest as of December 31, 2021	1,412,550	$ 12.01	8.46	$ 3,134,377
Options exercisable as of December 31, 2021	472,553	$ 25.55	7.10	$ 763,461

The assumptions used in the Black-Scholes option pricing model to determine the fair value of the employee stock option grants were as follows:

	Years Ended December 31,		
	2021	2020	2019
Expected term (in years)	5.50 – 6.08	5.50 – 6.08	5.51 – 6.07
Risk-free interest rate	0.6% – 1.3%	0.3% – 1.5%	1.4% – 2.6%
Expected volatility	86.3% – 104.8%	102.2% – 109.7%	97.2% – 105.4%
Expected dividend yield	0.0%	0.0%	0.0%

The assumptions used in the Black-Scholes option pricing model to determine the fair value of the ESPP offering were as follows:

	Years Ended December 31,		
	2021	2020	2019
Expected term (in years)	0.50	0.50	0.50
Risk-free interest rate	0.04% – 0.12%	0.1% – 1.6%	1.6% – 2.5%
Expected volatility	89.7% – 108.12%	89.7% – 143.2%	99.7% – 141.7%
Expected dividend yield	0.0%	0.0%	0.0%

Expected term. The expected term represents the period of time that options are expected to be outstanding. Because we do not have sufficient history of exercise behavior, we determine the expected life assumption using the simplified method, which is an average of the contractual term of the option and its vesting period.

Risk-free interest rate. We base the risk-free interest rate assumption on the U.S. Treasury's rates for U.S. Treasury zero-coupon bonds with maturities similar to those of the expected term of the award being valued.

Expected volatility. The expected volatility assumption is based on our historical volatility as well as the volatilities of a peer group of similar companies whose share prices are publicly available. The peer group was developed based on companies in the biotechnology industry.

Expected dividend yield. We base the expected dividend yield assumption on the fact that we have never paid cash dividends and have no present intention to pay cash dividends.

Restricted Stock Units

Occasionally, we grant restricted stock units to employees. The fair value of restricted stock is determined by the closing price of the Company's common stock reported on the Nasdaq Global Select Market on the date of grant. Restricted stock unit activity is summarized as follows:

	Number of Outstanding Restricted Stock Units	Weighted Average Grant Date Fair Value
Balance as of December 31, 2020	7,677	$ 5.32
Granted	4,000	$ 3.89
Released	(4,177)	$ 6.18
Balance as of December 31, 2021	7,500	$ 4.08

The allocation of stock-based compensation for all options, including performance options with market condition and restricted stock units is as follows (in thousands):

	Years Ended December 31,		
	2021	2020	2019
Research and development	$ 295	$ 254	$ 354
General and administrative	1,319	1,211	1,429
Total stock-based compensation expense	$ 1,614	$ 1,465	$ 1,783

The weighted-average grant date fair value per share of stock options granted by us, during the years ended December 31, 2021, 2020 and 2019 was $3.82, $3.39 and $5.67, respectively. The total grant date fair value of restricted stock units granted by us during the years ended December 31, 2021, 2020, and 2019 was approximately $16,000, $21,000 and $39,000, respectively. The aggregate intrinsic value of stock options exercised during the year ended December 31, 2021 was approximately $80,000. We did not have any options exercised during the years ended December 31, 2020 and 2019. The aggregate intrinsic value of restricted stock units released during the years ended December 31, 2021, 2020 and 2019 was approximately $31,000, $34,000 and $31,000, respectively. As of December 31, 2021, total unrecognized share-based compensation expense related to unvested stock options and restricted stock units was approximately $3.5 million and $20,000, respectively. These unrecognized costs for options and restricted stock units are expected to be recognized ratably over a weighted-average period of approximately 3.0 years and 2.6 years, respectively.

Warrants

Warrants outstanding for the purchase of common stock as of December 31, 2021 were as follows:

Number Outstanding	Exercise Price Per Share	Expiration Date
1,066	$ 281.50	July 2023
6,830	$ 43.93	November 2023
2,978	$ 50.37	June 2024
2,886	$ 51.98	December 2024
13,760		

Common Stock Reserved for Future Issuance

Common stock reserved for future issuance was as follows:

	December 31, 2021
Common stock warrants	13,760
Common stock options and restricted stock units	1,420,050
Shares available under the 2015 equity incentive plan	420,896
Shares available under the employee stock purchase plan	71,933
	1,926,639

8. Income Tax

Pretax losses were generated by both domestic and foreign operations as follows (in thousands):

	Years Ended December 31,		
	2021	2020	2019
United States	$ (33,316)	$ (15,950)	$ (23,315)
Foreign	(458)	(280)	(448)
Worldwide pre-tax loss	$ (33,774)	$ (16,230)	$ (23,763)

For the years ended December 31, 2021, 2020, and 2019, we did not record a provision for income taxes due to a full valuation allowance against our deferred taxes. A reconciliation of the expected statutory federal income tax provision to the actual income tax provision is summarized as follows (in thousands):

	Years Ended December 31,		
	2021	2020	2019
Expected income taxes benefit at federal statutory rate	$ (7,093)	$ (3,408)	$ (4,990)
State income taxes, net of federal benefit	(2,313)	(12)	(19)
Permanent items and other	592	169	49
Stock compensation	90	804	701
Research credits	(1,253)	(835)	(817)
Unrecognized tax benefits	500	334	327
Foreign rate differential	21	13	20
Change in tax rate	52	(7)	(49)
Change in valuation allowance	9,404	2,942	4,778
Income tax (benefit) expense	$ —	$ —	$ —

Deferred income taxes are provided for temporary differences in recognizing certain income and expense items for financial and tax reporting purposes. The deferred tax assets consisted primarily of the income tax benefits from net operating loss (NOL) carryforwards, research and development credits and capitalized research and development expenses, along with other accruals and reserves. Valuation allowances of $84.1 million and $74.6 million as of December 31, 2021 and 2020, respectively, have been recorded to offset deferred tax assets as realization of such assets does not meet the more-likely-than-not threshold under ASC 740, *Accounting for Income Taxes*.

Significant components of our deferred tax assets are summarized as follows (in thousands):

	December 31,	
	2021	2020
Deferred tax assets:		
Net operating loss carryforwards	$ 48,833	$ 41,203
Capitalized research and development expenses	18,086	17,007
Research credits and other state credits	13,695	12,954
Intangible assets	1,465	1,655
Reserve and accruals	641	544
Share-based compensation expense	1,369	1,253
Lease liability	290	472
Valuation allowance	(84,112)	(74,646)
Total deferred tax assets	$ 267	$ 442
Deferred tax liabilities:		
Right of use lease assets	(267)	(442)
Total deferred tax liabilities	(267)	(442)
Net deferred tax assets	$ —	$ —

As of December 31, 2021, we had federal NOL carryforwards of approximately $204.5 million, with $92.0 million of NOLs generated after December 31, 2017 carrying forward indefinitely and $112.5 million of NOLs that will begin to expire in 2025. NOLs generated after January 1, 2018 are subject to an 80% of taxable income limitation when utilized after December 31, 2020 in accordance with the Tax Cuts and Jobs Act of 2017 as modified by the Coronavirus Aid, Relief and Economic Security Act (CARES Act). We had state net operating loss carryforwards of approximately $192.0 million, and foreign net operating loss carryforwards of $8.7 million. The state net operating losses will begin to expire in 2021. The foreign net operating losses carry over indefinitely.

As of December 31, 2021, we had federal and state research and development credit carryforwards of approximately $6.5 million and $4.8 million, respectively, which begin to expire in 2026 for federal purposes and carry over indefinitely for state purposes. We had $12.5 million of federal Orphan Drug Credits as of December 31, 2021, which will begin to expire in 2035.

Utilization of the domestic NOL and research and development credit carryforwards may be subject to a substantial annual limitation due to ownership change limitations that may have occurred or that could occur in the future, as required by Sections 382 and 383 of the Internal Revenue Code of 1986, as amended (the Code), as well as similar state and foreign provisions. These ownership changes may limit the amount of NOL and research and development credit carryforwards that can be utilized annually to offset future taxable income and tax, respectively. In general, an “ownership change” as defined by Section 382 of the Code results from a transaction or series of transactions over a three-year period resulting in an ownership change of more than 50 percentage points of the outstanding stock of a company by certain stockholders. Since the Company’s formation, we raised capital through the issuance of capital stock on several occasions which on its own or combined with the purchasing stockholders’ subsequent disposition of those shares, has resulted in such an ownership change, and could result in an ownership change in the future.

Upon the occurrence of an ownership change under Section 382 as outlined above, utilization of the NOL and research and development credit carryforwards become subject to an annual limitation under Section 382 of the Code, which is determined by first multiplying the value of our stock at the time of the ownership change by the applicable long-term, tax-exempt rate, which could be subject to additional adjustments. Any limitation may result in expiration of a portion of our NOL or research and development credit carryforwards before utilization. Due to the existence of the valuation allowance, any impact to the NOL and research and development tax credit carryforwards from Section 382 analysis will be offset by a corresponding adjustment to valuation allowance, resulting in no tax provision impact.

We recognize a tax benefit from an uncertain tax position when it is more likely than not that the position will be sustained upon examination, including resolutions of any related appeals or litigation processes, based on the technical merits. Income tax positions must meet a more-likely-than-not recognition threshold to be recognized.

Our practice is to recognize interest and penalties related to income tax matters in income tax expense. We had no accrual for interest and penalties on our balance sheet and had not recognized interest or penalties in the consolidated statements of operations for the years ended December 31, 2021, 2020 and 2019.

Due to the existence of the valuation allowance, future changes in unrecognized tax benefits will not impact our effective tax rate.

Uncertain tax positions are evaluated based upon the facts and circumstances that exist at each reporting period. Subsequent changes in judgment based upon new information may lead to changes in recognition, derecognition, and measurement. Adjustments may result, for example, upon resolution of an issue with the taxing authorities, or expiration of a statute of limitations barring an assessment for an issue.

The activity related to our unrecognized tax benefits is summarized as follows (in thousands):

	December 31,		
	2021	2020	2019
Balance as of beginning of year	$ 21,707	$ 21,302	$ 19,643
Increase (decrease) related to prior year tax positions	(9)	3	—
Increase related to current year tax positions	534	402	1,659
Balance as of end of year	$ 22,232	$ 21,707	$ 21,302

We do not anticipate that the amount of unrecognized tax benefits as of December 31, 2021 will change within the next twelve months.

We are subject to taxation in the United States, Hong Kong and state jurisdictions. Our tax years from inception are subject to examination by the United States, Hong Kong and California authorities due to carry forward of unutilized NOLs and research and development credits.

9. Employee Benefits

401(k) Plan

We maintain a defined contribution 401(k) plan available to eligible employees. Employee contributions are voluntary and are determined on an individual basis, limited to the maximum amount allowable under federal tax regulations. In April 2015, our Board of Directors approved a policy, beginning on June 1, 2015, to match employee contributions equal to 50% of the participant's contribution of up to a maximum of 6% of the participant's annual salary. We made discretionary contributions totaling $0.2 million during each of the years ended December 31, 2021, 2020 and 2019.

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

We maintain disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act that are designed to ensure that information required to be disclosed in our periodic and current reports that we file with the SEC 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 Principal Executive Officer and Principal Financial Officer, as appropriate, to allow timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable and not absolute assurance of achieving the desired control objectives. In reaching a reasonable level of assurance, management necessarily is required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures. In addition, the design of any system of controls also is based in part upon certain assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions; over time, control may become inadequate because of changes in conditions, or the degree of compliance with policies or procedures may deteriorate. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected.

We carried out an evaluation, under the supervision and with the participation of our management, including our Principal Executive Officer and Principal Financial Officer, of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act. Based on this evaluation, our Principal Executive Officer and Principal Financial Officer concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of December 31, 2021.

Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting as such term is defined in Rules 13a-15(f) and 15-d-15(f) of the Exchange Act. Internal control over financial reporting is a process designed under the supervision and with the participation of our management, including our Principal Executive Officer and Principal Financial Officer, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with accounting principles generally accepted in the United States of America.

As of December 31, 2021, our management assessed the effectiveness of our internal control over financial reporting using the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in Internal Control – 2013 Integrated Framework (2013 Framework). Based on this assessment, our management concluded that our internal control over financial reporting was effective as of December 31, 2021.

This Annual Report does not include an attestation report of our registered public accounting firm under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)).

Changes in Internal Control Over Financial Reporting

During the quarter ended December 31, 2021, there have been no changes in our internal control over financial reporting, as such term is defined in Rules 13a-15(f) and 15d-15(f) promulgated under the Exchange Act, that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

None.

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

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

Except as set forth below, the information required by this item will be contained in our Definitive Proxy Statement to be filed with the SEC in connection with our 2022 Annual Meeting of Stockholders within 120 days after the end of the fiscal year ended December 31, 2021, and is incorporated herein by reference.

We have adopted a written code of ethics for directors, officers (including our principal executive officer, principal financial officer and principal accounting officer or persons performing similar functions) and employees, known as the Code of Business Conduct and Ethics. The Code of Business Conduct and Ethics is available on our website at *http://www.atyrpharma.com* under the Corporate Governance section of our Investors and Media page. If we make any substantive amendments to, or grant any waivers from, the Code of Business Conduct and Ethics for any officer or director, we will disclose the nature of such 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 contained in our Definitive Proxy Statement and is incorporated herein by reference.

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

The information required by this item will be contained in our Definitive Proxy Statement and is incorporated herein by reference.

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

The information required by this item will be contained in our Definitive Proxy Statement and is incorporated herein by reference.

Item 14. Principal Accountant Fees and Services.

The information required by this item will be contained in our Definitive Proxy Statement and is incorporated herein by reference.

PART IV

Item 15. Exhibit and Financial Statement Schedules.

(a) The following documents are filed as part of this Annual Report.

1. *Index list to Financial Statements*:

	Page
Report of Independent Registered Public Accounting Firm (PCAOB ID: 42)	67
Consolidated Balance Sheets	69
Consolidated Statements of Operations	70
Consolidated Statements of Comprehensive Loss	71
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2. *Financial Statement Schedules*.

Schedules have been omitted as all required information has been disclosed in the financial statements and related footnotes.

3. *Exhibits*.

The Exhibits listed in the Exhibit Index are filed as a part of this Annual Report.

EXHIBIT INDEX

Exhibit Number	Exhibit Title	Incorporated by Reference			
		Form	File No.	Exhibit	Filing Date
3.1	Restated Certificate of Incorporation of the Registrant	S-1/A	333-203272	3.2	May 1, 2015
3.2	Certificate of Amendment to Restated Certificate of Incorporation of the Registrant	8-K	001-37378	3.1	June 28, 2019
3.3	Certificate of Amendment to Restated Certificate of Incorporation of the Registrant	10-Q	001-37378	3.3	May 12, 2020
3.4	Certificate of Amendment to Restated Certificate of Incorporation of the Registrant	8-K	001-37378	3.1	May 4, 2021
3.5	Amended and Restated Bylaws of the Registrant	S-1/A	333-203272	3.4	April 27, 2015
3.6	Certificate of Designation of Preferences, Rights and Limitations of Class X Convertible Preferred Stock	8-K	001-37378	3.1	August 31, 2017
4.1	Specimen Common Stock Certificate	S-1/A	333-203272	4.1	April 27, 2015
4.2	Warrant to Purchase Stock issued to Silicon Valley Bank on July 24, 2013	S-1	333-203272	4.4	April 6, 2015
4.3	Warrant to Purchase Stock issued to Silicon Valley Bank on November 18, 2016	10-K	001-37378	4.5	March 16, 2017
4.4	Warrant to Purchase Stock issued to Solar Capital Ltd on November 18, 2016	10-K	001-37378	4.6	March 16, 2017
4.5	Warrant to Purchase Stock issued to Silicon Valley Bank on June 30, 2017	10-Q	001-37378	4.7	August 14, 2017
4.6	Warrant to Purchase Stock issued to Solar Capital Ltd on June 30, 2017	10-Q	001-37378	4.8	August 14, 2017
4.7	Warrant to Purchase Stock issued to Silicon Valley Bank on December 22, 2017	10-K	001-37378	4.8	March 20, 2018
4.8	Warrant to Purchase Stock issued to Solar Capital Ltd on December 22, 2017	10-K	001-37378	4.9	March 20, 2018
4.9	Registration Rights Agreement, by and between the Registrant and Aspire Capital Fund, LLC, dated September 11, 2020	8-K	001-37378	4.1	September 14, 2020
4.10	Description of Common Stock of the Registrant	10-K	001-37378	4.10	March 26, 2020
10.1*	2014 Stock Plan and forms of agreements thereunder	S-1/A	333-203272	10.1	April 27, 2015
10.2*	2015 Stock Option and Incentive Plan, as amended	8-K	001-37378	10.1	May 4, 2021
10.3*	Forms of agreement under 2015 Stock Option and Incentive Plan	S-1/A	333-203272	10.2	April 27, 2015
10.4	Lease by and between the Registrant and BMR-John Hopkins Court LLC, dated December 22, 2011	S-1	333-203272	10.9	April 6, 2015
10.5	First Amendment to Lease between the Registrant and BMR-3545-3575 JOHN HOPKINS LP (as successor-in-interest to BMR-John Hopkins Court LLC), dated January 4, 2017	10-K	001-37378	10.8	March 16, 2017
10.6	Form of Indemnification Agreement entered into between the Registrant and its directors	S-1/A	333-203272	10.12	April 27, 2015
10.7	Form of Indemnification Agreement entered into between the Registrant and its officers	S-1/A	333-203272	10.13	April 27, 2015

Exhibit Number	Exhibit Title	Incorporated by Reference			
		Form	File No.	Exhibit	Filing Date
10.8*	2015 Employee Stock Purchase Plan	S-1/A	333-203272	10.14	April 27, 2015
10.9*	Senior Executive Cash Incentive Bonus Plan	8-K	001-37378	10.1	January 29, 2016
10.10*	Executive Severance and Change in Control Policy	10-K	001-37378	10.16	March 30, 2016
10.11*	Registrant's Non-Qualified Stock Option Agreement for Non-Plan Inducement Grant	10-Q	001-37378	10.1	November 14, 2016
10.12	Second Amendment to Lease between the Registrant and BMR-3545-3575 John Hopkins LP (as successor-in-interest to BMR-John Hopkins Court, LLC), dated April 27, 2017	10-Q	001-37378	10.1	May 11, 2017
10.13*	Employment Agreement, dated November 1, 2017, by and between the Company and Sanjay S. Shukla, M.D., M.S.	10-Q	001-37378	10.4	November 14, 2017
10.14*	Employment Offer Letter by and between the Registrant and Jill M. Broadfoot, dated July 16, 2018	8-K	001-37378	10.1	August 1, 2018
10.15	Third Amendment to Lease between Registrant and BMR-3545-3575 John Hopkins LP (as successor-in interest to BMR-John Hopkins Court, LLC), dated July 30, 2018	10-Q	001-37378	10.1	November 11, 2018
10.16*	Employment Offer Letter by and between Registrant and Ms. Nancy Krueger, Esq., dated October 7, 2014	10-Q	001-37378	10.2	May 14, 2019
10.17†	Collaboration and License Agreement by and between Registrant and Kyorin Pharmaceutical Co., Ltd., dated January 6, 2020	S-1/A	333-235951	10.21	February 3, 2020
10.18	Common Stock Purchase Agreement, by and between the Registrant and Aspire Capital Fund, LLC, dated September 11, 2020	8-K	001-37378	99.1	September 14, 2020
10.19*	First Amendment to Employment Agreement dated February 5, 2021, by and between the Company and Sanjay S. Shukla, M.D., M.S.	10-K	001-37378	10.19	March 24, 2021
10.20**	Common Stock Capital on Demand™ Sales Agreement, between the Registrant and JonesTrading Institutional Services LLC	—	—	—	Filed herewith
21.1	Subsidiaries of the Registrant	S-1	333-203272	21.1	April 6, 2015
23.1	Consent of Independent Registered Public Accounting Firm	—	—	—	Filed herewith
24.1	Power of Attorney (included on signature page to this Annual Report)	—	—	—	Filed herewith
31.1#	Certification of Principal Executive Officer required by Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002	—	—	—	Filed herewith
31.2#	Certification of Principal Financial Officer required by Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002	—	—	—	Filed herewith
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	—	—	—	Filed herewith
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	—	—	—	Filed herewith
101.INS	Inline XBRL Instance Document	—	—	—	Filed herewith
101.SCH	Inline XBRL Taxonomy Extension Schema Document	—	—	—	Filed herewith
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document	—	—	—	Filed herewith

Exhibit Number	Exhibit Title	Incorporated by Reference			Filing Date
		Form	File No.	Exhibit	
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document	—	—	—	Filed herewith
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document	—	—	—	Filed herewith
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document	—	—	—	Filed herewith
104	Cover Page Interactive Data File (embedded within the Inline XBRL and contained in Exhibits 101)	—	—	—	Filed herewith

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* Indicates a management contract or compensatory plan, contract or arrangement.

** Originally filed as an exhibit to the Company's Annual Report on Form 10-K for the year ended December 31, 2021, and included herein solely to correct the exhibit hyperlink in that prior filing.

† Certain portions have been omitted because the Registrant has determined that the information is not material and would likely cause competitive harm to the Registrant if publicly disclosed.

The information in Exhibits 32.1 and 32.2 shall not be deemed "filed" for purposes of Section 18 of the Exchange Act, or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act or the Exchange Act (including this Annual Report on Form 10-K), unless the Registrant specifically incorporates the foregoing information into those documents by reference.

Item 16. Form 10-K Summary.

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

aTyr Pharma, Inc.

Date: March 15, 2022

By /s/ Sanjay S. Shukla
Sanjay S. Shukla, M.D., M.S.
President, Chief Executive Officer and Director
(Principal Executive Officer)

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Sanjay S. Shukla, M.D., M.S. and Jill M. Broadfoot, jointly and severally, and each of them, his or her true and lawful attorneys-in-fact, each with full power of substitution, for him or her in any and all capacities, to sign any amendments to this Annual Report on Form 10-K and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each of said attorneys-in-fact or their substitute or substitutes may do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Sanjay S. Shukla Sanjay S. Shukla, M.D., M.S.	President, Chief Executive Officer and Director *(Principal Executive Officer)*	March 15, 2022
/s/ Jill M. Broadfoot Jill M. Broadfoot	Chief Financial Officer *(Principal Financial and Accounting Officer)*	March 15, 2022
/s/ John K. Clarke John K. Clarke	Chairman of the Board	March 15, 2022
/s/ Timothy P. Coughlin Timothy P. Coughlin	Director	March 15, 2022
/s/ Jane A. Gross Jane A. Gross, Ph.D.	Director	March 15, 2022
/s/ Svetlana Lucas Svetlana Lucas, Ph.D.	Director	March 15, 2022
/s/ Paul Schimmel Paul Schimmel, Ph.D.	Director	March 15, 2022
/s/ Sara Zaknoen Sara Zaknoen	Director	March 15, 2022

ATYR PHARMA, INC.

Common Stock
($0.001 par value per share)

Capital on Demand™ Sales Agreement

March 23, 2021

JonesTrading Institutional Services LLC
757 Third Avenue, 23rd Floor
New York, NY 10017

Ladies and Gentlemen:

aTyr Pharma, Inc., a Delaware corporation (the "Company"), proposes, subject to the terms and conditions stated herein, to issue and sell from time to time to or through JonesTrading Institutional Services LLC ("JonesTrading"), as sales agent and/or principal ("Agent"), shares (the "Shares") of the Company's common stock, $0.001 par value per share (the "Common Stock"), having an aggregate offering price of up to $25,000,000 on the terms set forth in Section 2 of this Capital on Demand™ Sales Agreement (the "Agreement"). The Company agrees that whenever it determines to sell Shares directly to the Agent as principal, it will enter into a separate agreement (each, a "Terms Agreement") in substantially the form of Annex I hereto, relating to such sale in accordance with Section 3 of this Agreement.

Section 1. Representations and Warranties. Except as disclosed in the Registration Statement (as defined below), Prospectus (as defined below) or General Disclosure Package (as defined below), the Company represents and warrants to the Agent that as of the date of this Agreement and as of each Applicable Time (as defined in Section 1(a) below):

(a) Compliance with Registration Requirements. The Company has filed with the Securities and Exchange Commission (the "Commission") a registration statement under the Securities Act of 1933, as amended (the "1933 Act"), on Form S-3 (File No. 333-250095), in respect of the Company's Common Stock (including the Shares); such registration statement, and any post-effective amendment thereto, shall have become effective prior to the effectiveness of any Terms Agreement or instructions to sell shares delivered pursuant to Section 2(b) hereunder; and no stop order suspending the effectiveness of such registration statement or any part thereof shall have been issued and no proceeding for that purpose shall have been initiated or, to the knowledge of the Company, threatened by the Commission; the base prospectus filed as part of such registration statement is hereinafter called the "Basic Prospectus"; the various parts of such registration statement, including all exhibits thereto and any prospectus supplement relating to the Shares that is filed with the Commission and deemed by virtue of Rule 430B to be part of such registration statement, each as amended at the time such part of the registration statement became effective, are hereinafter collectively called the "Registration Statement"; the Company has prepared a prospectus supplement to the prospectus included as a part of such registration statement specifically relating to the Shares to be filed with the Commission pursuant to Rule 424(b) under the 1933 Act, hereinafter called the "Prospectus Supplement"; the Basic Prospectus, including all documents incorporated therein by reference, included in the Registration Statement, as it may be supplemented by the Prospectus Supplement, in the form in which such prospectus and/or Prospectus Supplement have most recently been filed by the Company with the Commission pursuant to Rule 424(b) under the Securities Act is herein called the "Prospectus"; any reference herein to the Basic Prospectus, the Prospectus Supplement or the Prospectus shall be deemed to refer to and include the documents incorporated by reference therein pursuant to Item 12 of Form S-3 under the 1933 Act; any reference to any amendment or supplement to the Basic Prospectus, the Prospectus Supplement or the Prospectus shall be deemed to refer to and include any post-effective amendment to the Registration Statement, any prospectus supplement relating to the Shares filed with the Commission pursuant to Rule 424(b) under the 1933 Act and any documents filed under the Securities Exchange Act of 1934, as amended (the "1934 Act"), and the rules and regulations of the Commission thereunder (the "1934 Act Regulations"), and incorporated therein, in each case after the date of the Basic Prospectus, the Prospectus

Supplement or the Prospectus, as the case may be; any reference to any amendment to the Registration Statement shall be deemed to refer to and include any annual report of the Company filed pursuant to Section 13(a) or 15(d) of the 1934 Act after the effective date of the Registration Statement that is incorporated by reference in the Registration Statement; and any "issuer free writing prospectus" as defined in Rule 433 under the 1933 Act relating to the Shares is hereinafter called an "Issuer Free Writing Prospectus".

No order preventing or suspending the use of the Basic Prospectus, the Prospectus Supplement, the Prospectus or any Issuer Free Writing Prospectus has been issued by the Commission, and the Basic Prospectus and the Prospectus Supplement, at the time of filing thereof, conformed in all material respects to the requirements of the 1933 Act and the rules and regulations of the Commission thereunder (the "1933 Act Regulations") and did not contain an untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein, in the light of the circumstances under which they were made, not misleading.

For the purposes of this Agreement, the "Applicable Time" means, with respect to any Shares, the time of sale of such Shares pursuant to this Agreement; the Prospectus and the applicable Issuer Free Writing Prospectus(es) issued at or prior to such Applicable Time, taken together (collectively, and, with respect to any Shares, together with the public offering price of such Shares, the "General Disclosure Package") as of each Applicable Time and each Settlement Date, will not include any untrue statement of a material fact or omit to state any material fact necessary in order to make the statements therein, in the light of the circumstances under which they were made, not misleading; and each applicable Issuer Free Writing Prospectus will not conflict with the information contained in the Registration Statement, the Prospectus Supplement or the Prospectus and each such Issuer Free Writing Prospectus, as supplemented by and taken together with the General Disclosure Package as of such Applicable Time, will not include any untrue statement of a material fact or omit to state any material fact necessary in order to make the statements therein, in the light of the circumstances under which they were made, not misleading.

(b) Incorporation of Documents by Reference. The documents incorporated or deemed to be incorporated by reference in the Registration Statement and the Prospectus, when they became effective or were filed with the Commission, as the case may be, complied in all material respects with the applicable requirements of the 1934 Act and the 1934 Act Regulations, and, when read together with the other information in the Prospectus, (a) at the time the Registration Statement became effective, (b) at the time the Prospectus was issued and (c) on the date of this Agreement, did not contain an untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein, in light of the circumstances under which they were made, not misleading.

(c) Independent Accountants. The accountants who certified the financial statements and supporting schedules included in the Registration Statement are independent public accountants as required by the 1933 Act and the 1933 Act Regulations.

(d) Financial Statements. The financial statements included or incorporated by reference in the Registration Statement, the General Disclosure Package and the Prospectus, together with the related schedules and notes, present fairly, in all material respects, the financial position of the Company and its consolidated Subsidiaries (as defined below) at the dates indicated and the statement of operations, stockholders' equity and cash flows of the Company and its consolidated Subsidiaries for the periods specified; said financial statements have been prepared in conformity with generally accepted accounting principles in the United States ("GAAP") applied on a consistent basis throughout the periods involved except as may be set forth in the notes included or incorporated by reference and except that unaudited financial statements may not contain footnotes required by GAAP. The supporting schedules, if any, present fairly, in all material respects, in accordance with GAAP the information required to be stated therein. The selected financial data and the summary financial information included in the Prospectus present fairly, in all material respects, the information shown therein and have been compiled on a basis consistent with that of the audited financial statements included or incorporated by reference in the Registration Statement. Any financial measures contained in the Registration Statement, the General Disclosure Package or the Prospectus, or incorporated by reference therein, that constitute "non-GAAP financial measures" (as such term is defined by the rules and regulations of the Commission) comply with Regulation G of the 1934 Act and Item 10 of Regulation S-K of the 1933 Act, to the extent applicable.

(e) No Material Adverse Change in Business. Since the respective dates as of which information is given in the Registration Statement, the General Disclosure Package or the Prospectus (A) there has been no material adverse change, or any development that could reasonably be expected to result in a material adverse change, in the condition, financial or otherwise, or in the earnings, business affairs or business prospects of the Company and its Subsidiaries considered as one enterprise, whether or not arising in the ordinary course of business (a "Material Adverse Effect"), (B) there have been no transactions entered into by the Company or any of its Subsidiaries, other than those in the ordinary course of business, which are material with respect to the Company and its Subsidiaries considered as one enterprise, and (C) there has been no dividend or distribution of any kind declared, paid or made by the Company on any class of its capital stock.

(f) Good Standing of the Company. The Company has been duly organized and is validly existing as a corporation in good standing under the laws of the jurisdiction of its organization and has corporate power and authority to own, lease and operate its properties and to conduct its business as described in the Prospectus and to enter into and perform its obligations under this Agreement; and the Company is duly qualified as a foreign corporation to transact business and is in good standing in each other jurisdiction in which such qualification is required, whether by reason of the ownership or leasing of property or the conduct of business, except where the failure so to qualify or to be in good standing would not result in a Material Adverse Effect.

(g) Good Standing of Subsidiaries. Each subsidiary listed on Schedule 1 hereto (each a "Subsidiary" and, collectively, the "Subsidiaries") has been duly organized and is validly existing as a corporation in good standing under the laws of the jurisdiction of its incorporation, has corporate power and authority to own, lease and operate its properties and to conduct its business as described in the Prospectus and is duly qualified as a foreign corporation to transact business and is in good standing in each jurisdiction in which such qualification is required, whether by reason of the ownership or leasing of property or the conduct of business, except where the failure so to qualify or to be in good standing would not result in a Material Adverse Effect; except as would not result in a Material Adverse Effect, all of the issued and outstanding capital stock of each such Subsidiary has been duly authorized and validly issued, is fully paid and non-assessable and is owned by the Company, directly or through subsidiaries, free and clear of any security interest, mortgage, pledge, lien, encumbrance, or adverse claim; none of the outstanding shares of capital stock of any Subsidiary was issued in violation of the preemptive or similar rights of any securityholder of such Subsidiary except where such failure would not result in a Material Adverse Effect. Any significant subsidiaries (as such term is defined in Rule 1-02 of Regulation S-X promulgated by the Commission), direct and indirect, of the Company are listed on Schedule 1 hereto.

(h) Capitalization. The shares of issued and outstanding Common Stock have been duly authorized and validly issued and are fully paid and non-assessable; none of the outstanding shares of capital stock was issued in violation of the preemptive or other similar rights of any securityholder of the Company. The Company's Common Stock has been registered pursuant to Section 12(b) of the 1934 Act and is listed on the Nasdaq Capital Market (the "Nasdaq"), and the Company has taken no action designed to terminate the registration or listing of the Common Stock from the Nasdaq, nor has the Company received any notification that the Commission or the Nasdaq is contemplating terminating such registration or listing.

(i) Authorization of Agreements. This Agreement and any Terms Agreement have been duly authorized by the Company. This Agreement has been, and any Terms Agreement will be, executed and delivered by the Company.

(j) Authorization and Description of Shares. The Shares have been duly authorized and reserved for issuance and sale pursuant to this Agreement and, when issued and delivered by the Company pursuant to this Agreement or any Terms Agreement against payment of the consideration set forth herein or therein, will be validly issued and fully paid and non-assessable; the Common Stock conforms to all statements relating thereto contained in the Prospectus and such description conforms to the rights set forth in the instruments defining the same; no holder of the Shares will be subject to personal liability by reason of being such a holder; and the issuance of the Shares is not subject to the preemptive or other similar rights of any securityholder of the Company.

(k) Absence of Defaults and Conflicts. (a) Neither the Company nor any of its Subsidiaries is in violation of its charter or by-laws or in default in the performance or observance of any obligation, agreement, covenant or condition contained in any contract, indenture, mortgage, deed of trust, loan or credit agreement, note,

lease or other agreement or instrument to which the Company or any of its Subsidiaries is a party or by which it or any of them may be bound, or to which any of the property or assets of the Company or any Subsidiary is subject (collectively, "Agreements and Instruments") except for such violations and defaults as would not have a Material Adverse Effect; (b)(i) and the execution, delivery and performance of this Agreement or of any Terms Agreement and the consummation of the transactions contemplated herein or in any Terms Agreement and in the Registration Statement (including the issuance and sale of the Shares and the use of the proceeds from the sale of the Shares as described in the Prospectus under the caption "Use of Proceeds") and compliance by the Company with its obligations hereunder have been duly authorized by all necessary corporate action and do not and will not, whether with or without the giving of notice or passage of time or both, conflict with or constitute a breach of, or default or Repayment Event (as defined below) under, or result in the creation or imposition of any lien, charge or encumbrance upon any property or assets of the Company or any Subsidiary pursuant to, the Agreements and Instruments, (ii) nor will such action result in any violation of the provisions of the charter or by-laws of the Company or any Subsidiary, (iii) nor will such action result in any violation of any applicable law, statute, rule, regulation, judgment, order, writ or decree of any government, government instrumentality or court, domestic or foreign, having jurisdiction over the Company or any Subsidiary or any of their assets, properties or operations. As used herein, a "Repayment Event" means any event or condition which gives the holder of any note, debenture or other evidence of indebtedness (or any person acting on such holder's behalf) the right to require the repurchase, redemption or repayment of all or a portion of such indebtedness by the Company or any Subsidiary.

(l) Absence of Labor Dispute. Except where the failure thereof would not result in a Material Adverse Effect, no labor dispute with the employees of the Company or any Subsidiary exists or, to the knowledge of the Company, is imminent, and the Company is not aware of any existing or imminent labor disturbance by the employees of any of its or any Subsidiary's principal suppliers, manufacturers, customers or contractors.

(m) Absence of Proceedings. There is no action, suit, proceeding, inquiry or investigation before or brought by any court or governmental agency or body, domestic or foreign, now pending, or, to the knowledge of the Company, threatened, against or affecting the Company or any Subsidiary, which would reasonably be expected to result in a Material Adverse Effect, or which might materially and adversely affect the consummation of the transactions contemplated in this Agreement or any Terms Agreement or the performance by the Company of its obligations hereunder or thereunder.

(n) Accuracy of Exhibits. There are no contracts or documents which are required to be described in the Registration Statement or the Prospectus or the documents incorporated by reference therein or to be filed as exhibits thereto which have not been so described and filed as required.

(o) Possession of Intellectual Property. Except where the failure thereof would not reasonably be expected to result in a Material Adverse Effect, (i) the Company and its Subsidiaries own or possess, or can acquire on reasonable terms, adequate patents, patent rights, licenses, inventions, copyrights, know-how (including trade secrets and other unpatented and/or unpatentable proprietary or confidential information, systems or procedures), trademarks, service marks, trade names or other intellectual property (collectively, "Intellectual Property") necessary to carry on the business now operated by them, and (ii) neither the Company nor any of its Subsidiaries has received any notice of any infringement of or conflict with asserted rights of others with respect to any Intellectual Property or of any facts or circumstances which would render any Intellectual Property invalid or inadequate to protect the interest of the Company or any of its Subsidiaries therein.

(p) Absence of Further Requirements. Except where the absence thereof would not result in a Material Adverse Effect, no filing with, or authorization, approval, consent, license, order, registration, qualification or decree of, any court or governmental authority or agency is necessary or required for the performance by the Company of its obligations hereunder, in connection with the offering, issuance or sale of the Shares hereunder or the consummation of the transactions contemplated by this Agreement or any Terms Agreement, except such as have been already obtained or as may be required under the 1933 Act or the 1933 Act Regulations or state securities laws or by the rules of the Nasdaq or the Financial Industry Regulatory Authority, Inc. ("FINRA").

(q) Absence of Manipulation. Neither the Company nor to the Company's knowledge any affiliate of the Company has taken, nor will the Company take, directly or indirectly, any action which is designed to or which

has constituted or which would be reasonably expected to cause or result in stabilization or manipulation of the price of any security of the Company to facilitate the sale or resale of the Shares.

(r) Possession of Licenses and Permits. The Company and each of its Subsidiaries have made all filings, applications, declarations and submissions required by, and own or possess all approvals, licenses, certificates, clearances, consents, exemptions, marks, notifications, orders, authorizations and permits issued by the appropriate local, state, federal or foreign regulatory agencies or bodies, including all such registrations, approvals, certificates, authorizations and permits required by the United States Food and Drug Administration (the "FDA") which are required for the ownership of their respective properties or the conduct of their current respective businesses as described in the Registration Statement, General Disclosure Package and the Prospectus (each, a "Governmental License") except where any failures to possess or any noncompliance would not, singly or in the aggregate, have a Material Adverse Effect and neither the Company nor any of its Subsidiaries has received any notice of any revocation, modification or cancellation of, any such Governmental License, which, individually or in the aggregate, if the subject of an unfavorable decision, ruling or finding, would reasonably be expected to result in a Material Adverse Effect. Where required by applicable laws and regulations of the FDA, the Company has submitted to the FDA an Investigational New Drug Application or amendment or supplement thereto for each clinical trial it has conducted or sponsored or is conducting or sponsoring, except where such failure would not, singly or in the aggregate, reasonably be expected to have a Material Adverse Effect; all such submissions were in material compliance with applicable laws and rules and regulations when submitted and no material deficiencies have been asserted by the FDA with respect to any such submissions, except any deficiencies which could not, singly or in the aggregate, reasonably be expected to have a Material Adverse Effect.

(s) Title to Property. Except where the failure thereof would result in a Material Adverse Effect, to the Company's knowledge, (i) the Company and its Subsidiaries have good and marketable title to all real property owned by the Company and its Subsidiaries and good title to all other properties owned by it that are material to the business of the Company, in each case, free and clear of all mortgages, pledges, liens, security interests, claims, restrictions or encumbrances of any kind except such as do not, singly or in the aggregate, affect the value of such property and do not interfere with the use made and proposed to be made of such property by the Company or any of its Subsidiaries; and (ii) all of the leases and subleases material to the business of the Company and its Subsidiaries, considered as one enterprise, and under which the Company or any of its Subsidiaries holds properties described in the Prospectus, are in full force and effect, and neither the Company nor any Subsidiary has any notice of any material claim of any sort that has been asserted by anyone adverse to the rights of the Company or any Subsidiary under any of the leases or subleases mentioned above, or affecting or questioning the rights of the Company or such Subsidiary to the continued possession of the leased or subleased premises under any such lease or sublease.

(t) Investment Company Act. The Company is not required, and upon the issuance and sale of the Shares as herein contemplated and the application of the net proceeds therefrom as described in the Prospectus will not be required, to register as an "investment company" within the meaning of the Investment Company Act of 1940, as amended.

(u) Environmental Laws. Except as would not reasonably be expected to, singly or in the aggregate, result in a Material Adverse Effect: (A) neither the Company nor any of its Subsidiaries is in violation of any federal, state, local or foreign statute, law, rule, regulation, ordinance, code, policy or rule of common law or any judicial or administrative interpretation thereof, including any judicial or administrative order, consent, decree or judgment, relating to pollution or protection of human health, the environment (including, without limitation, ambient air, surface water, groundwater, land surface or subsurface strata) or wildlife, including, without limitation, laws and regulations relating to the release or threatened release of chemicals, pollutants, contaminants, wastes, toxic substances, hazardous substances, petroleum or petroleum products, asbestos-containing materials or mold (collectively, "Hazardous Materials") or to the manufacture, processing, distribution, use, treatment, storage, disposal, transport or handling of Hazardous Materials (collectively, "Environmental Laws"), (B) the Company and its Subsidiaries have all permits, authorizations and approvals required under any applicable Environmental Laws and are each in compliance with their requirements, (C) there are no pending or, to the Company's knowledge threatened administrative, regulatory or judicial actions, suits, demands, demand letters, claims, liens, notices of noncompliance or violation, investigation or proceedings relating to any Environmental Law against the Company or any of its Subsidiaries and (D) there are no events or circumstances of which the Company is aware that would reasonably be expected to form the basis of an order for clean-up or remediation, or an action, suit or proceeding by

any private party or governmental body or agency, against or affecting the Company or any of its Subsidiaries relating to Hazardous Materials or any Environmental Laws.

(v) Registration Rights. There are no persons with registrations rights or other similar rights to have any securities registered pursuant to the Registration Statement, except for such rights as have been duly waived.

(w) Accounting Controls and Disclosure Controls. The Company and each of its Subsidiaries maintain a system of internal accounting controls sufficient to provide reasonable assurances that (A) transactions are executed in accordance with management's general or specific authorization; (B) transactions are recorded as necessary to permit preparation of financial statements in conformity with GAAP and to maintain accountability for assets; (C) access to assets is permitted only in accordance with management's general or specific authorization; and (D) the recorded accountability for assets is compared with the existing assets at reasonable intervals and appropriate action is taken with respect to any differences. Since the end of the Company's most recent audited fiscal year, the Company is not aware of any (1) material weakness in the Company's internal control over financial reporting (whether or not remediated) and (2) change in the Company's internal control over financial reporting that has materially affected, or is reasonably likely to materially affect, the Company's internal control over financial reporting.

The Company and its consolidated Subsidiaries employ disclosure controls and procedures that are designed to ensure that information required to be disclosed by the Company in the reports that it files or submits under the 1934 Act is recorded, processed, summarized and reported, within the time periods specified in the Commission's rules and forms, and is accumulated and communicated to the Company's management, including its principal executive officer or officers and principal financial officer or officers, as appropriate, to allow timely decisions regarding disclosure.

(x) S-3 Eligibility. (A)(i) At the time of filing the Registration Statement and (ii) at the time of the most recent amendment thereto for the purposes of complying with Section 10(a)(3) of the 1933 Act (whether such amendment was by post-effective amendment, incorporated report filed pursuant to Section 13 or 15(d) of the 1934 Act or form of prospectus), the Company met the then applicable requirements for use of Form S-3 under the 1933 Act and (B) at the earliest time after the filing of the Registration Statement that the Company or JonesTrading acting under a valid Terms Agreement made a bona fide offer (within the meaning of Rule 164(h)(2) under the 1933 Act) of the Shares, the Company was not an "ineligible issuer" as defined in Rule 405 under the 1933 Act.

(y) No Commissions. Neither the Company nor any of its Subsidiaries is a party to any contract, agreement or understanding with any person (other than as contemplated by this Agreement or any Terms Agreement) that would give rise to a valid claim against the Company or any of its Subsidiaries or the Agent for a brokerage commission, finder's fee or like payment in connection with the offering and sale of the Shares.

(z) Deemed Representation. Any certificate signed by any officer of the Company delivered to the Agent or to counsel for the Agent pursuant to or in connection with this Agreement or any Terms Agreement shall be deemed a representation and warranty by the Company to the Agent as to the matters covered thereby as of the date or dates indicated in such certificate.

(aa) Compliance with the Sarbanes-Oxley Act. The Company is in compliance in all material respects with all applicable provisions of the Sarbanes-Oxley Act of 2002 and the rules and regulations promulgated in connection therewith, including Section 402 related to loans and Sections 302 and 906 related to certifications.

(bb) Intentionally omitted.

(cc) Payment of Taxes. All United States federal income tax returns of the Company and its Subsidiaries required by law to be filed have been filed and all taxes shown by such returns or otherwise assessed, which are due and payable, have been paid, except assessments against which appeals have been or will be promptly taken and as to which adequate reserves have been provided and except where the failure to do so would not reasonably be expected to have a Material Adverse Effect. The Company and its Subsidiaries have filed all other tax returns that are required to have been filed by them pursuant to applicable foreign, state, local or other law and have paid all taxes due pursuant to such returns or pursuant to any assessment received by the Company and its

Subsidiaries, except for such taxes, if any, as are being contested in good faith and as to which adequate reserves have been provided and except where the failure to do so would reasonably be expected to have a Material Adverse Effect.

(dd) Insurance. The Company and its Subsidiaries carry or are entitled to the benefits of insurance, with financially sound and reputable insurers, in such amounts and covering such risks as is generally maintained by companies of established repute engaged in the same or similar business, and all such insurance is in full force and effect. The Company has no reason to believe that it or any Subsidiary will not be able (A) to renew its existing insurance coverage as and when such policies expire or (B) to obtain comparable coverage from similar institutions as may be necessary or appropriate to conduct its business as now conducted and at a cost that would not result in a Material Adverse Effect. During the prior three year period, neither of the Company nor any Subsidiary has been denied any material insurance coverage which it has sought or for which it has applied.

(ee) Statistical and Market-Related Data. Any statistical and market-related data included in the Registration Statement, the General Disclosure Package and the Prospectus are based on or derived from sources that the Company believes to be reliable and accurate, and, where required, the Company's good faith estimates that are made on the basis of such data from such sources.

(ff) Foreign Corrupt Practices Act. Neither the Company nor, to the knowledge of the Company, any director, officer, agent, employee, affiliate or other person acting on behalf of the Company or any of its Subsidiaries is aware of or has taken any action, directly or indirectly, that would result in a violation by such persons of the Foreign Corrupt Practices Act of 1977, as amended, and the rules and regulations thereunder (the "FCPA"), including, without limitation, making use of the mails or any means or instrumentality of interstate commerce corruptly in furtherance of an offer, payment, promise to pay or authorization of the payment of any money, or other property, gift, promise to give, or authorization of the giving of anything of value to any "foreign official" (as such term is defined in the FCPA) or any foreign political party or official thereof or any candidate for foreign political office, in contravention of the FCPA and the Company and, to the knowledge of the Company, its affiliates have conducted their businesses in compliance with the FCPA and have instituted and maintain policies and procedures designed to ensure, and which are reasonably expected to continue to ensure, continued compliance therewith.

(gg) Money Laundering Laws. The operations of the Company are and have been conducted at all times in compliance with applicable financial recordkeeping and reporting requirements of the Currency and Foreign Transactions Reporting Act of 1970, as amended, the money laundering statutes of all applicable jurisdictions, the applicable rules and regulations thereunder and any related or similar rules, regulations or guidelines, issued, administered or enforced by any governmental agency (collectively, the "Money Laundering Laws") and no action, suit or proceeding by or before any court or governmental agency, authority or body or any arbitrator involving the Company with respect to the Money Laundering Laws is pending or, to the knowledge of the Company, threatened.

(hh) OFAC. Neither the Company nor, to the knowledge of the Company, any director, officer, agent, employee, affiliate or person acting on behalf of the Company is currently subject to any U.S. sanctions administered by the Office of Foreign Assets Control of the U.S. Treasury Department ("OFAC"); and the Company will not directly or indirectly use the proceeds of this offering, or lend, contribute or otherwise make available such proceeds to any Subsidiary, joint venture partner or other person or entity, for the purpose of financing the activities of any person whom the Company has knowledge is currently subject to any U.S. sanctions administered by OFAC.

(ii) Tests and Preclinical and Clinical Studies. The Company has operated and currently is in compliance with the United States Federal Food, Drug, and Cosmetic Act, all applicable rules and regulations of the FDA and other federal, state, local and foreign governmental bodies exercising comparable authority, except where the failure to so operate or be in compliance would not reasonably be expected to have a Material Adverse Effect. The preclinical and clinical studies conducted by or, to the Company's knowledge, on behalf of the Company that are described in the Registration Statement and the Prospectus were, and if still pending, are being, conducted in all material respects in accordance with experimental protocols, procedures and controls pursuant to, where applicable, accepted professional and scientific standards for products or product candidates comparable to those being developed by the Company; the descriptions of the tests and preclinical and clinical studies, and results thereof,

conducted by or, to the Company's knowledge on the behalf of the Company contained in the Registration Statement, the General Disclosure Package and the Prospectus are accurate and complete in all material respects; the Company is not aware of any trials or studies not described or referred to in the Registration Statement, the General Disclosure Package and the Prospectus, the results of which reasonably call into question the results described or referred to in the Registration Statement, the General Disclosure Package and the Prospectus; the Company is not in receipt of any notices or correspondence from the FDA or any foreign, state or local governmental body exercising comparable authority that reasonably call into question results of the trials or studies described or referred to in the Registration Statement, the General Disclosure Package and the Prospectus; and the Company has not received any notice or correspondence from the FDA or any foreign, state or local governmental body exercising comparable authority requiring the termination, suspension, or clinical hold of any tests or preclinical or clinical studies, or such notice or correspondence from any Institutional Review Board or comparable authority requiring the termination or suspension of a clinical study, conducted by or on behalf of the Company, which termination, suspension, or clinical hold would reasonably be expected to have a Material Adverse Effect.

(jj) IT Systems. (i)(x) To the knowledge of Company, there has been no security breach or other compromise of any of the Company's information technology and computer systems, networks, hardware, software, data (including the data of their respective customers, employees, suppliers, vendors and any third party data maintained by or on behalf of them), equipment or technology (collectively, "IT Systems and Data") and (y) the Company has not been notified of, and has no knowledge of any event or condition that would reasonably be expected to result in, any security breach or other compromise to their IT Systems and Data, except as would not, in the case of this clause (i), individually or in the aggregate, reasonably be expected to have a Material Adverse Effect; and (ii) the Company is presently in material compliance with all applicable laws or statutes and all judgments, orders, rules and regulations of any court or arbitrator or governmental or regulatory authority, internal policies and contractual obligations relating to the privacy and security of IT Systems and Data and to the protection of such IT Systems and Data from unauthorized use, access, misappropriation or modification, except as would not, in the case of this clause (ii), individually or in the aggregate, have a Material Adverse Effect.

Section 2. Sale and Delivery of Shares.

(a)Subject to the terms and conditions set forth herein, the Company agrees to issue and sell exclusively through the Agent acting as sales agent or directly to the Agent acting as principal from time to time, and the Agent agrees to use its commercially reasonable efforts to sell as sales agent for the Company, the Shares. Sales of the Shares, if any, through the Agent acting as sales agent or directly to the Agent acting as principal may be made in negotiated transactions or transactions that are deemed to be "at the market offerings" as defined in Rule 415 of the 1933 Act. Anything to the contrary notwithstanding in this Agreement, without the Company's prior written consent (which may be included explicit authorization in a Terms Agreement), the Agent may not place Shares by any method other than those deemed to be an "at the market offering" as defined in Rule 415 of the 1933 Act. Nothing contained herein restricts, nor may be deemed to restrict, the Company from undertaking another offering of its securities pursuant to a separate registration under the 1933 Act (or any exemption from such registration), or another offering under the Registration Statement, provided the Company complies with Section 3(p).

(b) Subject to the applicable Terms Agreement or instructions to sell shares delivered pursuant to this Section 2(b), the Shares to be sold pursuant to this Agreement are to be sold on a daily basis or otherwise as shall be agreed to by the Company and the Agent on that trading day (other than a day on which the Nasdaq is scheduled to close prior to its regular weekday closing time, each, a "Trading Day") that the Company has satisfied its obligations under Section 6 of this Agreement and that the Company has instructed the Agent to make such sales. For the avoidance of doubt, the foregoing limitation shall not apply to sales solely to employees or security holders of the Company or its Subsidiaries, or to a trustee or other person acquiring such securities for the accounts of such persons in which JonesTrading is acting for the Company in a capacity other than as Agent under this Agreement. On any Trading Day, the Company may instruct the Agent by telephone (confirmed promptly by telecopy or email, which confirmation will be promptly acknowledged by the Agent) as to the maximum aggregate dollar value or number of Shares to be sold by the Agent on such day (in any event not in excess of the number available for issuance under the Prospectus and the currently effective Registration Statement) and the minimum price per Share at which such Shares may be sold. Subject to the terms and conditions hereof, the Agent shall use its commercially reasonable efforts to sell as sales agent all of the Shares so designated by the Company and in the

manner and on the terms so designated in writing by the Company. The Company and the Agent each acknowledge and agree that (A) there can be no assurance that the Agent will be successful in selling the Shares, (B) the Agent will incur no liability or obligation to the Company or any other person or entity if they do not sell Shares for any reason other than a failure by the Agent to use its commercially reasonable efforts consistent with its normal trading and sales practices and applicable law and regulations to sell such Shares as required by this Agreement, and (C) the Agent shall be under no obligation to purchase Shares on a principal basis except as otherwise specifically agreed by each of the Agent and the Company pursuant to a Terms Agreement. In the event of a conflict between the terms of this Agreement and the terms of a Terms Agreement, the terms of such Terms Agreement will control.

(c) Notwithstanding the foregoing, the Company shall not authorize the issuance and sale of, and the Agent as sales agent shall not be obligated to use its commercially reasonable efforts to sell, any Shares (i) at a price lower than the minimum price therefor authorized from time to time, or (ii) in a number in excess of the number or maximum aggregate dollar value of Shares authorized from time to time to be issued and sold under this Agreement, in each case, by the Company's board of directors, or a duly authorized committee thereof, and notified to the Agent in writing. In addition, the Company may, upon notice to the Agent, suspend the offering of the Shares or the Agent may, upon notice to the Company, suspend the offering of the Shares with respect to which the Agent is acting as sales agent for any reason and at any time; provided, however, that such suspension or termination shall not affect or impair the parties' respective obligations with respect to the Shares sold hereunder prior to the giving of such notice. Any notice given pursuant to the preceding sentence may be given by telephone (confirmed promptly by telecopy or email, which confirmation will be promptly acknowledged).

(d) The gross sales price of any Shares sold pursuant to this Agreement by the Agent acting as sales agent of the Company shall be the market price prevailing at the time of sale for shares of the Company's Common Stock sold by the Agent on the Nasdaq or otherwise, at prices relating to prevailing market prices or at negotiated prices. The compensation payable to the Agent for sales of Shares with respect to which the Agent acts as sales agent shall be equal to up to 3.0% of the gross sales price of the Shares for amounts of Shares sold pursuant to this Agreement. The Company may sell Shares to the Agent, acting as principal, at a price agreed upon with the Agent at the relevant Applicable Time and pursuant to a separate Terms Agreement. The remaining proceeds, after further deduction for any transaction fees imposed by any governmental, regulatory or self-regulatory organization in respect of such sales, shall constitute the net proceeds to the Company for such Shares (the "Net Proceeds"). The Agent shall notify the Company as promptly as practicable if any deduction referenced in the preceding sentence will be required.

(e) If acting as a sales agent hereunder, the Agent shall provide written confirmation to the Company following the close of trading on the Nasdaq, each day in which Shares are sold under this Agreement setting forth the number of Shares sold on such day, the aggregate gross sales proceeds of the Shares, the Net Proceeds to the Company and the compensation payable by the Company to such Agent with respect to such sales.

(f) Under no circumstances shall the aggregate offering price or number, as the case may be, of Shares sold pursuant to this Agreement and any Terms Agreement exceed the aggregate offering price or number, as the case may be, of shares of Common Stock (i) set forth in the preamble paragraph of this Agreement, (ii) available for issuance under the Prospectus and the then currently effective Registration Statement, (iii) authorized from time to time to be issued and sold under this Agreement or any Terms Agreement by the Company's board of directors, or a duly authorized committee thereof, and notified to the Agent in writing or (iv) authorized but unissued pursuant to the Company's certificate of incorporation. In addition, under no circumstances shall any Shares with respect to which the Agent acts as sales agent be sold at a price lower than the minimum price therefor authorized from time to time by the Company's board of directors, or a duly authorized committee thereof, and notified to the Agent in writing.

(g) Settlement for sales of Shares pursuant to this Section 2 will occur on the second business day that is also a Trading Day following the trade date on which such sales are made, unless another date shall be agreed to by the Company and the Agent (each such day, a "Settlement Date"). On each Settlement Date, the Shares sold through the Agent for settlement on such date shall be delivered by the Company to the Agent against payment of the Net Proceeds from the sale of such Shares. Settlement for all Shares shall be effected by book-entry delivery of Shares to the Agent's account at The Depository Trust Company against payments by the Agent of the Net Proceeds from the sale of such Shares in same day funds delivered to an account designated by the Company. If the

Company shall default on its obligation to deliver Shares on any Settlement Date, the Company shall, in addition to any indemnification obligation pursuant to Section 7, pay the Agent any commission to which it would otherwise be entitled absent such default.

(h) Notwithstanding any other provision of this Agreement, the Company and the Agent agree that no sales of Shares shall take place, and the Company shall not request the sale of any Shares that would be sold, and the Agent shall not be obligated to sell, during any period in which the Company is, or would reasonably be deemed to be, in possession of material non-public information.

(i) Any obligation of the Agent to use its commercially reasonable efforts to sell the Shares on behalf of the Company as sales agent shall be subject to the continuing accuracy of the representations and warranties of the Company herein, to the performance by the Company of its obligations hereunder and to the continuing satisfaction of the additional conditions specified in Section 6 of this Agreement.

Section 3. Covenants. The Company agrees with the Agent:

(a) During any period when the delivery of a prospectus is required in connection with the offering or sale of Shares (whether physically or through compliance with Rule 153 or 172, or in lieu thereof, a notice referred to in Rule 173(a) under the 1933 Act), (i) to make no further amendment or any supplement to the Registration Statement or the Basic Prospectus (other than an amendment or supplement relating to an offering of the Company's securities which is unrelated to the offering of the Shares hereunder) prior to any Settlement Date which shall be disapproved by the Agent promptly after reasonable notice thereof and to advise the Agent, promptly after it receives notice thereof, of the time when any amendment to the Registration Statement has been filed or becomes effective or any amendment or supplement to the Basic Prospectus (other than an amendment or supplement relating to an offering of the Company's securities which is unrelated to the offering of the Shares hereunder) has been filed and to furnish the Agent with copies thereof, (ii) to file promptly all other material required to be filed by the Company with the Commission pursuant to Rule 433(d) under the 1933 Act, (iii) to file promptly all reports and any definitive proxy or information statements required to be filed by the Company with the Commission pursuant to Section 13(a), 13(c), 14 or 15(d) of the 1934 Act, (iv) to advise the Agent, promptly after it receives notice thereof, of the issuance by the Commission of any stop order or of any order preventing or suspending the use of the Prospectus or other prospectus in respect of the Shares, of the suspension of the qualification of the Shares for offering or sale in any jurisdiction, of the initiation or threatening of any proceeding for any such purpose, or of any request by the Commission for the amending or supplementing of the form of the Registration Statement or the Prospectus or for additional information, and (v) in the event of the issuance of any such stop order or of any such order preventing or suspending the use of the Prospectus in respect of the Shares or suspending any such qualification, to promptly use its commercially reasonable efforts to obtain the withdrawal of such order; and in the event of any such issuance of a notice of objection, promptly to take such reasonable steps as may be necessary to permit offers and sales of the Shares by the Agent, which may include, without limitation, amending the Registration Statement or filing a new registration statement, at the Company's expense (references herein to the Registration Statement shall include any such amendment or new registration statement). Notwithstanding the foregoing, the Company shall not be obligated to furnish copies of any report or statement filed with the Commission to the extent it is available on the Commission's Electronic Data-Gathering, Analysis, and Retrieval System ("EDGAR").

(b) Promptly from time to time to take such action as the Agent may reasonably request to qualify the Shares for offering and sale under the securities laws of such jurisdictions as the Agent may request and to comply with such laws so as to permit the continuance of sales and dealings therein in such jurisdictions for as long as may be necessary to complete the sale of the Shares, provided that in connection therewith the Company shall not be required to qualify as a foreign corporation or to file a general consent to service of process in any jurisdiction; and to promptly advise the Agent of the receipt by the Company of any notification with respect to the suspension of the qualification of the Shares for offer or sale in any jurisdiction or the initiation or threatening of any proceeding for such purpose.

(c) During any period when the delivery of a prospectus is required (whether physically or through compliance with Rules 153 or 172, or in lieu thereof, a notice referred to in Rule 173(a) under the 1933 Act) in connection with the offering or sale of Shares, the Company will make available to the Agent, as soon as practicable

after the execution of this Agreement, and thereafter from time to time furnish to the Agent, copies of the most recent Prospectus in such quantities and at such locations as the Agent may reasonably request for the purposes contemplated by the 1933 Act. During any period when the delivery of a prospectus is required (whether physically or through compliance with Rules 153 or 172, or in lieu thereof, a notice referred to in Rule 173(a) under the 1933 Act) in connection with the offering or sale of Shares, and if at such time any event shall have occurred as a result of which the Prospectus as then amended or supplemented would include an untrue statement of a material fact or omit to state any material fact necessary in order to make the statements therein, in the light of the circumstances under which they were made when such Prospectus is delivered, not misleading, or, if for any other reason it shall be necessary during such same period to amend or supplement the Prospectus or to file under the 1934 Act any document incorporated by reference in the Prospectus in order to comply with the 1933 Act or the 1934 Act, to notify the Agent and to file such document and to prepare and furnish without charge to the Agent as many written and electronic copies as the Agent may from time to time reasonably request of an amended Prospectus or a supplement to the Prospectus which will correct such statement or omission or effect such compliance. Notwithstanding the foregoing, the Company shall not be required to furnish any document to the extent such document is available on EDGAR.

(d) To make generally available to its securityholders as soon as practicable, but in any event not later than sixteen months after the effective date of the Registration Statement (as defined in Rule 158(c) under the 1933 Act), an earnings statement of the Company and its Subsidiaries (which need not be audited) complying with Section 11(a) of the 1933 Act and the rules and regulations of the Commission thereunder (including, at the option of the Company, Rule 158).

(e) To pay the required Commission filing fees relating to the Shares within the time required by Rule 456(a) under the 1933 Act and otherwise in accordance with Rule 457(o) under the 1933 Act.

(f) To use the Net Proceeds received by it from the sale of the Shares pursuant to this Agreement and any Terms Agreement in the manner specified in the General Disclosure Package.

(g) In connection with the offering and sale of the Shares, the Company will file with the Nasdaq all documents and notices, and make all certifications, required by the Nasdaq of companies that have securities that are listed or quoted on the Nasdaq and will maintain such listings or quotations.

(h) To not take, directly or indirectly, and to use commercially reasonable efforts to cause its affiliates (as defined in Rule 405 of the 1933 Act Regulations) to refrain from taking, any action designed to cause or result in, or that has constituted or might reasonably be expected to constitute, under the 1934 Act or otherwise, the stabilization or manipulation of the price of any securities of the Company to facilitate the sale or resale of the Shares.

(i) In each Annual Report on Form 10-K or Quarterly Report on Form 10-Q filed by the Company in respect of any quarter in which sales of Shares were made by or through the Agent under this Agreement or any Terms Agreement (each date on which any such document is filed, and any date on which an amendment to any such document is filed, a "Company Periodic Report Date"), the Company shall set forth with regard to such quarter the approximate number of Shares sold through the Agent under this Agreement or any Terms Agreement and the Net Proceeds received by the Company with respect to sales of Shares pursuant to this Agreement or any Terms Agreement.

(j) Upon commencement of the offering of Shares under this Agreement (the "Commencement Date") and each time the Shares are delivered to the Agent as principal on a Settlement Date and promptly after each (i) date the Registration Statement or the Prospectus shall be amended or supplemented (other than (1) by an amendment or supplement providing solely for the determination of the terms of the Shares, (2) in connection with the filing of a prospectus supplement that contains solely the information set forth in Section 3(i), (3) in connection with the filing of any current reports on Form 8-K (other than any current reports on Form 8-K which contain financial statements, supporting schedules or other financial data, including any current report on Form 8-K under Item 2.02 of such form that is considered "filed" under the 1934 Act) or (4) by a prospectus supplement relating to the offering of other securities (including, without limitation, other shares of Common Stock)) (each such date, a "Registration Statement Amendment Date") and (ii) Company Periodic Report Date, the Company will furnish or

cause to be furnished forthwith to the Agent a certificate dated the date of effectiveness of such amendment or the date of filing with the Commission of such supplement or other document, as the case may be, in a form reasonably satisfactory to the Agent to the effect that the statements contained in the certificate referred to in Section 6(e) of this Agreement which were last furnished to the Agent are true and correct at the time of such amendment, supplement or filing, as the case may be, as though made at and as of such time (except that such statements shall be deemed to relate to the Registration Statement, the General Disclosure Package and the Prospectus as amended and supplemented to such time) or, in lieu of such certificate, a certificate of the same tenor as the certificate referred to in said Section 6(e), but modified as necessary to relate to the Registration Statement and the Prospectus as amended and supplemented, or to the document incorporated by reference into the Prospectus, to the time of delivery of such certificate. As used in this paragraph, to the extent there shall be an Applicable Time on or following the date referred to in clause (i) or (ii) above, promptly shall be deemed to be on or prior to the next succeeding Applicable Time. Notwithstanding the forgoing, the Company shall not be required to deliver any such certificate at any time there is no Terms Agreement or instructions to sell shares delivered pursuant to this Section 2(b) then in effect; provided, however, that such a certificate shall then be required to be delivered to the Agent prior to any further sales of Shares under this Agreement covering the period which would most recently have been required but for this sentence.

(k) On the Commencement Date and each time the Shares are delivered to the Agent as principal on a Settlement Date pursuant to a Terms Agreement, and promptly after each (i) Registration Statement Amendment Date and (ii) filing by the Company of a Company Periodic Report, the Company will furnish or cause to be furnished to the Agent and to counsel to the Agent the written opinion and letter of each Company Counsel (as defined below) or other counsel reasonably satisfactory to the Agent, dated the date of effectiveness of such amendment or the date of filing with the Commission of such supplement or other document, as the case may be, in a form and substance reasonably satisfactory to the Agent and its counsel, of the same tenor as the opinions and letters referred to in Section 6(c) of this Agreement, but modified as necessary to relate to the Registration Statement, the General Disclosure Package and the Prospectus as amended and supplemented, or to the document incorporated by reference into the Prospectus, to the time of delivery of such opinion and letter or, in lieu of such opinion and letter, counsel last furnishing such letter to the Agent shall furnish such Agent with a letter substantially to the effect that the Agent may rely on such last opinion and letter to the same extent as though each were dated the date of such letter authorizing reliance (except that statements in such last letter shall be deemed to relate to the Registration Statement and the Prospectus as amended and supplemented to the time of delivery of such letter authorizing reliance). As used in this paragraph, to the extent there shall be an Applicable Time on or following the date referred to in clause (i) or (ii) above, promptly shall be deemed to be on or prior to the next succeeding Applicable Time. Notwithstanding the forgoing, the Company shall not be required to furnish or cause to be furnished any such opinion or letter at any time there is no Terms Agreement or instructions to sell shares delivered pursuant to Section 2(b) then in effect; provided, however, that such an opinion or letter shall then be required to be furnished to the Agent prior to any further sales of Shares under this Agreement covering the period which would most recently have been required but for this sentence, and following the Agent being furnished with the first opinion(s) pursuant to this Section 3(k), subsequent opinions or letters furnished pursuant to this Section 3(k) shall only consist of customary “negative assurance” letters.

(l) On the Commencement Date and each time the Shares are delivered to the Agent as principal on a Settlement Date pursuant to a Terms Agreement, and promptly after each (i) Registration Statement Amendment Date (other than a Registration Statement Amendment date that occurs in connection with any filing of a Quarterly Report on Form 10-Q) and (ii) filing by the Company of a Company Annual Report on Form 10-K, the Company will cause Ernst & Young LLP, or other independent accountants reasonably satisfactory to the Agent, to furnish to the Agent a letter, dated the date of effectiveness of such amendment or the date of filing of such supplement or other document with the Commission, as the case may be, in form reasonably satisfactory to the Agent and its counsel, of the same tenor as the letter referred to in Section 6(d) hereof, but modified as necessary to relate to the Registration Statement, the General Disclosure Package and the Prospectus, as amended and supplemented, or to the document incorporated by reference into the Prospectus, to the date of such letter. As used in this paragraph, to the extent there shall be an Applicable Time on or following the date referred to in clause (i) or (ii) above, promptly shall be deemed to be on or prior to the next succeeding Applicable Time. Notwithstanding the forgoing, the Company shall not be required to furnish or cause to be furnished any such letter at any time there is no Terms Agreement or instructions to sell shares delivered pursuant to Section 2(b) then in effect; provided, however, that

such a letter shall then be required to be furnished to the Agent prior to any further sales of Shares under this Agreement covering the period which would most recently have been required but for this sentence.

(m) The Company consents to the Agent trading in the Company's Common Stock for the Agent's own account and for the account of its clients at the same time as sales of Shares occur pursuant to this Agreement or any Terms Agreement, provided that at all times the Agent is in compliance with Regulation M under the 1934 Act with respect to the Common Stock and provided that in no event shall the Agent trade the Common Stock for its or its affiliates' proprietary accounts.

(n) [Intentionally Omitted]

(o) The Company will cooperate timely with any reasonable due diligence review conducted by the Agent or its counsel from time to time in connection with the transactions contemplated hereby or in any Terms Agreement, including, without limitation, and upon reasonable notice providing information and making available documents and appropriate corporate officers, during regular business hours and at the Company's principal offices, as the Agent may reasonably request.

(p) During the time any instruction to sell shares delivered pursuant to Section 2(b) hereof or any Terms Agreement is in effect, the Company will not, without giving the Agent at least three business days' prior written notice specifying the nature of the proposed sale and the date of such proposed sale and the Agent suspending activity under this program for such period of time as requested by the Company, (A) offer, pledge, announce the intention to sell, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant for the sale of, lend or otherwise transfer or dispose of, directly or indirectly, any shares of Common Stock or securities convertible into or exchangeable or exercisable for or repayable with Common Stock, or file any registration statement under the 1933 Act with respect to any of the foregoing (other than a shelf registration statement under Rule 415 under the 1933 Act, a registration statement on Form S-8 or post-effective amendment to the Registration Statement) or (B) enter into any swap or other agreement or any transaction that transfers in whole or in part, directly or indirectly, any of the economic consequence of ownership of the Common Stock, or any securities convertible into or exchangeable or exercisable for or repayable with Common Stock, whether any such swap or transaction described in clause (A) or (B) above is to be settled by delivery of Common Stock or such other securities, in cash or otherwise. The foregoing sentence shall not apply to (x) any securities issuable upon the exercise or conversion of warrants, options, convertible securities or other rights either in existence prior to the date of this Agreement or issued thereafter in compliance with this Section 3(p), (y) the Shares to be offered and sold through the Agent pursuant to this Agreement or any Terms Agreement and (z) equity incentive awards approved by the board of directors of the Company or the compensation committee thereof or the issuance of Common Stock upon exercise thereof.

(q) If immediately prior to the third anniversary (the "Renewal Deadline") of the initial effective date of the Registration Statement, any of the Shares remain unsold, the Company will, prior to the Renewal Deadline file, if it has not already done so and is eligible to do so, an "automatic shelf registration statement" (as defined in Rule 405 under the 1933 Act) relating to the Shares, in a form reasonably satisfactory to the Agent. If the Company is not eligible to file an automatic shelf registration statement, the Company will, prior to the Renewal Deadline, if it has not already done so, file a new shelf registration statement relating to the Shares, in a form reasonably satisfactory to the Agent, and will use its commercially reasonable efforts to cause such registration statement to be declared effective within 60 days after the Renewal Deadline. The Company will use commercially reasonable efforts to take all other action necessary or appropriate to permit the issuance and sale of the Shares to continue as contemplated in the expired registration statement relating to the Shares. References herein to the Registration Statement shall include such new automatic shelf registration statement or such new shelf registration statement, as the case may be.

Section 4. Free Writing Prospectus.

(a) (i)The Company represents and agrees that without the prior consent of the Agent (which consent may not be unreasonably withheld, delayed or conditioned), it has not made and will not make any offer relating to the Shares that would constitute a "free writing prospectus" as defined in Rule 405 under the 1933 Act; and

(ii) the Agent represents and agrees that, without the prior consent of the Company (which consent may not be unreasonably withheld, delayed or conditioned), it has not made and will not make any offer relating to the Shares that would constitute a free writing prospectus required to be filed with the Commission.

(b) The Company has complied and will comply with the requirements of Rule 433 under the 1933 Act applicable to any Issuer Free Writing Prospectus (including any free writing prospectus identified in Section 4(a) hereof), including timely filing with the Commission or retention where required and legending.

Section 5. Payment of Expenses. The Company covenants and agrees with the Agent that the Company will pay or cause to be paid the following: (i) the fees, disbursements and expenses of the Company's counsel and accountants in connection with the registration of the Shares under the 1933 Act and all other expenses in connection with the preparation, printing and filing of the Registration Statement, the Basic Prospectus, Prospectus Supplement, any Issuer Free Writing Prospectus and the Prospectus and amendments and supplements thereto and the mailing and delivering of copies thereof to the Agent; (ii) the cost of printing or producing this Agreement or any Terms Agreement, any Blue Sky and Legal Investment Memoranda, closing documents (including any compilations thereof) and any other documents in connection with the offering, purchase, sale and delivery of the Shares; (iii) all expenses in connection with the qualification of the Shares for offering and sale under state securities laws as provided in Section 3(b) hereof, including the reasonable fees and disbursements of counsel for the Agent in connection with such qualification and in connection with the Blue Sky and Legal Investment Surveys; (iv) any filing fees incident to, and the reasonable fees and disbursements of counsel for the Agent in connection with, any required review by FINRA of the terms of the sale of the Shares; (v) the cost of preparing the Shares; (vi) the costs and charges of any transfer agent or registrar or any dividend distribution agent; (vii) the reasonable fees and disbursements of counsel to the Agent up to $45,000 (which amount shall include all fees and disbursements of such counsel described in clauses (iii) and (iv) above) and quarterly disbursements of counsel to the Agent up to $10,000 per calendar year; and (ix) all other costs and expenses incident to the performance of its obligations hereunder which are not otherwise specifically provided for in this Section. It is understood, however, that, except as provided in this Section, and Section 7 hereof, the Agent will pay all of its own costs and expenses, including the fees of its counsel, transfer taxes on resale of any of the Shares by it, and any advertising expenses connected with any offers it may make.

Section 6. Conditions of Agent's Obligation. The obligations of the Agent hereunder shall be subject, in its discretion, to the condition that all representations and warranties and other statements of the Company herein or in certificates of any officer of the Company delivered pursuant to the provisions hereof are true and correct as of the time of the execution of this Agreement, the date of any executed Terms Agreement and as of each Registration Statement Amendment Date, Company Periodic Report Date, Applicable Time and Settlement Date, to the condition that the Company shall have performed all of its obligations hereunder theretofore to be performed, and the following additional conditions:

(a) The Prospectus Supplement shall have been filed with the Commission pursuant to Rule 424(b) under the 1933 Act in accordance with Section 3(a) hereof, any other material required to be filed by the Company pursuant to Rule 433(d) under the 1933 Act shall have been filed with the Commission within the applicable time periods prescribed for such filings by Rule 433; no stop order suspending the effectiveness of the Registration Statement or any part thereof shall have been issued and no proceeding for that purpose shall have been initiated or threatened by the Commission and no notice of objection of the Commission to the use of the form of the Registration Statement or any post-effective amendment thereto pursuant to Rule 401(g)(2) under the 1933 Act shall have been received; no stop order suspending or preventing the use of the Prospectus or any Issuer Free Writing Prospectus shall have been initiated or threatened by the Commission; and all requests for additional information on the part of the Commission shall have been complied with to the reasonable satisfaction of the Agent.

(b) On every date specified in Section 3(k) hereof and on such other dates as reasonably requested by Agent, Duane Morris LLP, counsel for the Agent, shall have furnished to the Agent such written opinion or opinions, dated as of such date, with respect to such matters as the Agent may reasonably request, and such counsel shall have received such papers and information as they may reasonably request to enable them to pass upon such matters.

(c) On every date specified in Section 3(k) hereof, Cooley LLP, counsel for the Company, shall have furnished to the Agent written opinion or opinions, dated as of such date, in form and substance reasonably satisfactory to the Agent (it being understood and agreed that, other than the first such opinion furnished to the Agent, such opinions shall consist of a customary "negative assurance" letter).

(d) At the dates specified in Section 3(l) hereof, the independent accountants of the Company who have certified the financial statements of the Company and its Subsidiaries included or incorporated by reference in the Registration Statement, the General Disclosure Package and the Prospectus shall have furnished to the Agent a letter dated as of the date of delivery thereof and addressed to the Agent in form and substance reasonably satisfactory to the Agent and its counsel, containing statements and information of the type ordinarily included in accountants' "comfort letters" to underwriters with respect to the financial statements of the Company and its Subsidiaries included or incorporated by reference in the Registration Statement, the General Disclosure Package and the Prospectus.

(e) Prior to commencement of the offering of Shares under this Agreement, the Agent shall have received a certificate, signed on behalf of the Company by its corporate Secretary, in form and substance satisfactory to the Agent and its counsel, to the effect that (A) each of the charter and bylaws of the Company (as the same may be amended and/or restated) is true and complete, has not been modified and is in full force and effect, and (B) the resolutions of the Company's board of directors relating to the sales of Shares pursuant to this Agreement are in full force and effect and have not been modified.

(f) On each date specified in Section 3(j), the Agent shall have received a certificate of executive officers of the Company, one of whom shall be the Chief Financial Officer, Chief Accounting Officer, Treasurer, or Executive Vice President in the area of capital markets and investments, dated as of the date thereof, to the effect that (A) there has been no Material Adverse Effect since the date as of which information is given in the General Disclosure Package and the Prospectus as then amended or supplemented, (B) the representations and warranties in Section 1 hereof are true and correct as of such date and (C) the Company has complied with all of the agreements entered into in connection with the transaction contemplated herein and satisfied all conditions on its part to be performed or satisfied hereunder.

(g) [Intentionally Omitted]

(h) The Company shall have complied with the provisions of Section 3(c) hereof with respect to the timely furnishing of prospectuses.

(i) On such dates as reasonably requested by the Agent, the Company shall have conducted due diligence sessions, in form and substance reasonably satisfactory to the Agent.

(j) All filings with the Commission required by Rule 424 under the 1933 Act to have been filed by each Applicable Time or related Settlement Date shall have been made within the applicable time period prescribed for such filing by Rule 424 (without reliance on Rule 424(b)(8)).

(k) The Shares shall have received approval for listing or quotation on the Nasdaq prior to the first Settlement Date.

(l) Prior to any Settlement Date, the Company shall have furnished to the Agent such further information, documents or certificates as the Agent may reasonably request.

Section 7. Indemnification.

(a) The Company will indemnify and hold harmless the Agent against any losses, claims, damages or liabilities, joint or several, to which the Agent may become subject, under the 1933 Act or otherwise, insofar as such losses, claims, damages or liabilities (or actions in respect thereof) arise out of or are based upon an untrue statement or alleged untrue statement of a material fact contained in the Registration Statement, the Basic Prospectus, the Prospectus Supplement or the Prospectus or any amendment or supplement thereto, any Issuer Free Writing

Prospectus or any "issuer information" filed or required to be filed pursuant to Rule 433(d) under the 1933 Act, or arise out of or are based upon the omission or alleged omission to state therein a material fact required to be stated therein or necessary to make the statements therein not misleading, and will reimburse the Agent for any legal or other expenses reasonably incurred by the Agent in connection with investigating or defending any such action or claim as such expenses are incurred; provided, however, that the Company shall not be liable in any such case to the extent that any such loss, claim, damage or liability arises out of or is based upon an untrue statement or alleged untrue statement or omission or alleged omission made in the Registration Statement, the Basic Prospectus, the Prospectus Supplement or the Prospectus, or any amendment or supplement thereto, or any Issuer Free Writing Prospectus, in reliance upon and in strict conformity with written information furnished to the Company by the Agent expressly for use therein.

(b) The Agent will indemnify and hold harmless the Company against any losses, claims, damages or liabilities to which the Company may become subject, under the 1933 Act or otherwise, insofar as such losses, claims, damages or liabilities (or actions in respect thereof) arise out of or are based upon an untrue statement or alleged untrue statement of a material fact contained in the Registration Statement, the Basic Prospectus, the Prospectus Supplement or the Prospectus, or any amendment or supplement thereto, or any Issuer Free Writing Prospectus, or arise out of or are based upon the omission or alleged omission to state therein a material fact required to be stated therein or necessary to make the statements therein not misleading, in each case to the extent, but only to the extent, that such untrue statement or alleged untrue statement or omission or alleged omission was made in the Registration Statement, the Basic Prospectus, the Prospectus Supplement or the Prospectus, or any such amendment or supplement thereto, or any Issuer Free Writing Prospectus, in reliance upon and in strict conformity with written information furnished to the Company by the Agent expressly for use therein; and will reimburse the Company for any legal or other expenses reasonably incurred by the Company in connection with investigating or defending any such action or claim as such expenses are incurred.

(c) Promptly after receipt by an indemnified party under subsection (a) or (b) above of notice of the commencement of any action, such indemnified party shall, if a claim in respect thereof is to be made against the indemnifying party under such subsection, notify the indemnifying party in writing of the commencement thereof; but the omission so to notify the indemnifying party shall not relieve it from any liability which it may have to any indemnified party otherwise than under such subsection except and then only to the extent such indemnifying party is materially prejudiced thereby. In case any such action shall be brought against any indemnified party and it shall notify the indemnifying party of the commencement thereof, the indemnifying party shall be entitled to participate therein and, to the extent that it shall wish, jointly with any other indemnifying party similarly notified, to assume the defense thereof, with counsel reasonably satisfactory to such indemnified party, and, after notice from the indemnifying party to such indemnified party of its election so to assume the defense thereof, the indemnifying party shall not be liable to such indemnified party under this Section 7 for any legal expenses of other counsel or any other expenses, in each case subsequently incurred by such indemnified party, in connection with the defense thereof other than reasonable costs of investigation. No indemnifying party shall, without the written consent of the indemnified party, effect the settlement or compromise of, or consent to the entry of any judgment with respect to, any pending or threatened action or claim in respect of which indemnification or contribution may be sought hereunder (whether or not the indemnified party is an actual or potential party to such action or claim) unless such settlement, compromise or judgment (i) includes an unconditional release of the indemnified party from all liability arising out of such action or claim and (ii) does not include a statement as to or an admission of fault, culpability or a failure to act, by or on behalf of any indemnified party.

(d) If the indemnification provided for in this Section 7 is unavailable to hold harmless an indemnified party under subsection (a) or (b) above in respect of any losses, claims, damages or liabilities (or actions in respect thereof) referred to therein, then each indemnifying party shall contribute to the amount paid or payable by such indemnified party as a result of such losses, claims, damages or liabilities (or actions in respect thereof) in such proportion as is appropriate to reflect the relative benefits received by the Company on the one hand and the Agent on the other from the offering of the Shares to which such loss, claim, damage or liability (or action in respect thereof) relates. If, however, the allocation provided by the immediately preceding sentence is not permitted by applicable law, then each indemnifying party shall contribute to such amount paid or payable by such indemnified party in such proportion as is appropriate to reflect not only such relative benefits but also the relative fault of the Company on the one hand and the Agent on the other in connection with the statements or omissions which resulted in such losses, claims, damages or liabilities (or actions in respect thereof), as well as any other relevant equitable

considerations. The relative benefits received by the Company on the one hand and the Agent on the other shall be deemed to be in the same proportion as the total net proceeds from the offering (before deducting expenses) received by the Company bear to the total commissions received by the Agent. The relative fault shall be determined by reference to, among other things, whether the untrue or alleged untrue statement of a material fact or the omission or alleged omission to state a material fact relates to information supplied by the Company on the one hand or the Agent on the other and the parties' relative intent, knowledge, access to information and opportunity to correct or prevent such statement or omission. The Company and the Agent agree that it would not be just and equitable if contribution pursuant to this subsection (d) were determined by pro rata allocation or by any other method of allocation which does not take account of the equitable considerations referred to above in this subsection (d). The amount paid or payable by an indemnified party as a result of the losses, claims, damages or liabilities (or actions in respect thereof) referred to above in this subsection (d) shall be deemed to include any legal or other expenses reasonably incurred by such indemnified party in connection with investigating or defending any such action or claim. Notwithstanding the provisions of this subsection (d), the Agent shall not be required to contribute any amount in excess of the amount by which the total compensation received by the Agent with respect to sales of the Shares sold by it to the public exceeds the amount of any damages which the Agent has otherwise been required to pay by reason of such untrue or alleged untrue statement or omission or alleged omission. No person guilty of fraudulent misrepresentation (within the meaning of Section 11(f) of the 1933 Act) shall be entitled to contribution from any person who was not guilty of such fraudulent misrepresentation.

(e) The obligations of the Company under this Section 7 shall be in addition to any liability which the Company may otherwise have and shall extend, upon the same terms and conditions, to the directors, officers, employees, attorneys and agents of the Agent and to each person, if any, who controls the Agent within the meaning of the 1933 Act and each broker dealer affiliate of the Agent; and the obligations of the Agent under this Section 7 shall be in addition to any liability which the Agent may otherwise have and shall extend, upon the same terms and conditions, to each director, officer, employee, attorney and agent of the Company and to each person, if any, who controls the Company within the meaning of the 1933 Act.

Section 8. Representations, Warranties and Agreements to Survive Delivery. The respective indemnities, agreements, representations, warranties and other statements of the Company and the Agent, as set forth in this Agreement or made by or on behalf of them, respectively, pursuant to this Agreement, shall remain in full force and effect, regardless of any investigation (or any statement as to the results thereof) made by or on behalf of the Agent or any controlling person of the Agent, or the Company, or any officer or director or controlling person of the Company, and shall survive delivery of and payment for the Shares.

Section 9. No Advisory or Fiduciary Relationship. The Company acknowledges and agrees that (i) the Agent is acting solely in the capacity of an arm's length contractual counterparty to the Company with respect to the offering of Shares contemplated hereby (including in connection with determining the terms of such offering) and (ii) the Agent has not assumed an advisory or fiduciary responsibility in favor of the Company with respect to the offering contemplated hereby or the process leading thereto (irrespective of whether the Agent has advised or is currently advising the Company on other matters) or any other obligation to the Company except the obligations expressly set forth in this Agreement and (iii) the Company has consulted its own legal and financial advisors to the extent it deemed appropriate. The Company agrees that it will not claim that the Agent has rendered advisory services of any nature or respect, or owe a fiduciary or similar duty to the Company, in connection with such transaction or the process leading thereto.

Section 10. Termination.

(a) The Company shall have the right, by giving written notice as hereinafter specified, to terminate this Agreement in its sole discretion at any time. Any such termination shall be without liability of any party to any other party, except that (i) with respect to any pending sale through the Agent for the Company, the obligations of the Company, including in respect of compensation of the Agent, shall remain in full force and effect notwithstanding such termination; and (ii) the provisions of Section 1, Section 5, Section 7, Section 8, Section 14 and Section 15 of this Agreement shall remain in full force and effect notwithstanding such termination.

(b) The Agent shall have the right, by giving written notice as hereinafter specified, to terminate this Agreement in its sole discretion at any time. Any such termination shall be without liability of any party to any

other party, except that (i) with respect to any pending sale through the Agent for the Company, the obligations of the Agent shall remain in full force and effect through completion of the sale notwithstanding such termination; and (ii) the provisions of Section 1, Section 5, Section 7, Section 8, Section 14 and Section 15 of this Agreement shall remain in full force and effect notwithstanding such termination.

(c) Unless earlier terminated pursuant to this Section 10, this Agreement shall automatically terminate upon the issuance and sale of all of the Shares by the Agent on the terms and subject to the conditions set forth herein except any termination pursuant to this clause (c) shall in all cases be deemed to provide that Section 1, Section 5, Section 7, Section 8, Section 14 and Section 15 of this Agreement shall remain in full force and effect.

(d) This Agreement shall remain in full force and effect until and unless terminated pursuant to Section 10(a), (b) or (c) above or otherwise by mutual agreement of the parties; provided that any such termination by mutual agreement or pursuant to this clause (c) shall in all cases be deemed to provide that Section 1, Section 5(b), Section 7, Section 8, Section 14 and Section 15 of this Agreement shall remain in full force and effect.

(e) Any termination of this Agreement shall be effective on the date specified in such notice of termination; provided that such termination shall not be effective until the close of business on the date of receipt of such notice by the Agent or the Company, as the case may be. If such termination shall occur prior to the Settlement Date for any sale of Shares, such sale shall settle in accordance with the provisions of Section 2(h) hereof.

(f) In the case of any purchase by the Agent pursuant to a Terms Agreement, the Agent may terminate this Agreement, at any time at or prior to the Settlement Date of such purchase (i) if there has been, since the time of execution of this Agreement or since the respective dates as of which information is given in the General Disclosure Package or the Prospectus, any Material Adverse Effect, or (ii) if there has occurred any material adverse change in the financial markets in the United States or the international financial markets, any outbreak of hostilities or escalation thereof or other calamity or crisis or any change or development involving a prospective change in national or international political, financial or economic conditions, in each case the effect of which is such as to make it, in the judgment of the Agent, impracticable or inadvisable to market the Shares or to enforce contracts for the sale of Shares, or (iii) if trading in any securities of the Company has been suspended or materially limited by the Commission or the Nasdaq, or if trading generally on the Nasdaq or the New York Stock Exchange has been suspended or materially limited, or minimum or maximum prices for trading have been fixed, or maximum ranges for prices have been required, by any of said exchanges or by such system or by order of the Commission, FINRA or any other governmental authority, or (iv) a material disruption has occurred in commercial banking or securities settlement or clearance services in the United States, or (v) if a banking moratorium has been declared by either Federal or New York authorities.

Section 11. Notices. All statements, requests, notices and agreements hereunder shall be in writing, and if to JonesTrading shall be delivered or sent by mail, telex or facsimile transmission to:

JonesTrading Institutional Services LLC
900 Island Park Drive, Suite 160
Daniel Island, SC 29492
Attention: Burke Cook
Email: Burke@jonestrading.com

and

Duane Morris LLP
1540 Broadway
New York, NY 10036
Attn: Dean M. Colucci
E-mail: dmcolucci@duanemorris.com

and if to the Company to:

aTyr Pharma, Inc.

3545 John Hopkins Court, Suite 250
San Diego, CA 92121
Attention: Jill Broadfoot
Email: jbroadfoot@atyrpharma.com

with a copy to:

Cooley LLP
4401 Eastgate Mall
San Diego, California 92121
Attention: Sean Clayton
E-mail: sclayton@cooley.com

Any such statements, requests, notices or agreements shall take effect upon receipt thereof.

Section 12. Parties. This Agreement shall be binding upon, and inure solely to the benefit of, the Agent and the Company and, to the extent provided in Sections 7 and 8 hereof, the officers, directors, employees, attorneys and agents of the Company and the Agent and each person who controls the Company or the Agent, and their respective heirs, executors, administrators, successors and assigns, and no other person shall acquire or have any right under or by virtue of this Agreement. No purchaser of Shares through the Agent shall be deemed a successor or assign by reason merely of such purchase.

Section 13. Time of the Essence. Time shall be of the essence of this Agreement. As used herein, the term "business day" shall mean any day when the Commission's office in Washington, D.C. is open for business.

Section 14. Waiver of Jury Trial. The Company and the Agent hereby irrevocably waive, to the fullest extent permitted by applicable law, any and all right to jury trial by jury in any legal proceeding arising out of or relating to this Agreement or the transactions contemplated hereby.

Section 15. Governing Law. THIS AGREEMENT SHALL BE GOVERNED BY AND CONSTRUED IN ACCORDANCE WITH THE LAWS OF THE STATE OF NEW YORK WITHOUT REFERENCE TO ITS PRINCIPLES OF CONFLICTS OF LAW.

Section 16. Counterparts. This Agreement and any Terms Agreement may be executed by any one or more of the parties hereto and thereto in any number of counterparts, each of which shall be deemed to be an original, but all such respective counterparts shall together constitute one and the same instrument. This Agreement and any Terms Agreement may be delivered by any party by facsimile or other electronic transmission.

Section 17. Severability. The invalidity or unenforceability of any Section, paragraph or provision of this Agreement shall not affect the validity or enforceability of any other Section, paragraph or provision hereof. If any Section, paragraph or provision of this Agreement is for any reason determined to be invalid or unenforceable, there shall be deemed to be made such minor changes (and only such minor changes) as are necessary to make it valid and enforceable.

[Signature Page Follows]

If the foregoing is in accordance with your understanding of our agreement, please sign and return to the Company a counterpart hereof, whereupon this instrument, along with all counterparts, will become a binding agreement between the Agent and the Company in accordance with its terms.

Very truly yours,

ATYR PHARMA, INC.

By: _____
Name:
Title:

Accepted as of the date hereof:

JONESTRADING INSTITUTIONAL SERVICES LLC

By: _____
Name:
Title:

Schedule 1

Subsidiaries

Pangu BioPharma Limited

ATYR PHARMA, INC.

Common Stock
($0.001 par value per share)

TERMS AGREEMENT

JonesTrading Institutional Services LLC
757 Third Avenue, 23rd Floor
New York, NY 10017

Ladies and Gentlemen:

aTyr Pharma, Inc., a Delaware corporation (the "Company"), proposes, subject to the terms and conditions stated herein and in the Capital on Demand™ Sales Agreement, dated March 23, 2021 (the "Sales Agreement"), between the Company and JonesTrading Institutional Services LLC (the "Agent"), to issue and sell to the Agent the securities specified in the Schedule hereto (the "Purchased Securities") [, and solely for the purpose of covering over-allotments, to grant to the Agent the option to purchase the additional securities specified in the Schedule hereto (the "Additional Securities")]*.

[The Agent shall have the right to purchase from the Company all or a portion of the Additional Securities as may be necessary to cover over-allotments made in connection with the offering of the Purchased Securities, at the same purchase price per share to be paid by the Agent to the Company for the Purchased Securities. This option may be exercised by the Agent at any time (but not more than once) on or before the thirtieth day following the date hereof, by written notice to the Company. Such notice shall set forth the aggregate number of shares of Additional Securities as to which the option is being exercised, and the date and time when the Additional Securities are to be delivered (such date and time being herein referred to as the "Option Closing Date"); provided, however, that the Option Closing Date shall not be earlier than the Time of Delivery (as set forth in the Schedule hereto) nor earlier than the second business day after the date on which the option shall have been exercised nor later than the fifth business day after the date on which the option shall have been exercised. Payment of the purchase price for the Additional Securities shall be made at the Option Closing Date in the same manner and at the same office as the payment for the Purchased Securities.]*

Each of the provisions of the Sales Agreement not specifically related to the solicitation by the Agent, as agent of the Company, of offers to purchase securities is incorporated herein by reference in its entirety, and shall be deemed to be part of this Terms Agreement to the same extent as if such provisions had been set forth in full herein. Each of the representations and warranties set forth therein shall be deemed to have been made at and as of the date of this Terms Agreement [and] [,] the Applicable Time [and any Option Closing Date]*, except that each representation and warranty in Section 1 of the Sales Agreement which makes reference to the Prospectus (as therein defined) shall be deemed to be a representation and warranty as of the date of the Sales Agreement in relation to the Prospectus, and also a representation and warranty as of the date of this Terms Agreement [and] [,] the Settlement Date [and any Option Closing Date]* in relation to the Prospectus as amended and supplemented to relate to the Purchased Securities.

An amendment to the Registration Statement (as defined in the Sales Agreement), or a supplement to the Prospectus, as the case may be, relating to the Purchased Securities [and the Additional Securities]*, in the form heretofore delivered to the Agent is now proposed to be filed with the Securities and Exchange Commission.

Subject to the terms and conditions set forth herein and in the Sales Agreement which are incorporated herein by reference, the Company agrees to issue and sell to the Agent and the latter agrees to purchase from the

Company the number of shares of the Purchased Securities at the time and place and at the purchase price set forth in the Schedule hereto.

If the foregoing is in accordance with your understanding of our agreement, please sign and return to the Company a counterpart hereof, whereupon this instrument, along with all counterparts, will become a binding agreement between the Agent and the Company in accordance with its terms.

Very truly yours,

ATYR PHARMA, INC.

By:

Name:
Title:

Accepted as of the date hereof:

JONESTRADING INSTITUTIONAL SERVICES LLC

By:

Name:
Title:

* Include only if the Agent has an over-allotment option.

ATYR PHARMA, INC.

Code of Business Conduct and Ethics

Introduction

Purpose and Scope

The Board of Directors of aTyr Pharma, Inc. (the "Company") established this Code of Business Conduct and Ethics (this "Code") to aid the Company's directors, officers and employees in making ethical and legal decisions when conducting the Company's business and performing their day-to-day duties.

The Company's Board of Directors (the "Board") or a committee of the Board is responsible for administering the Code. The Board has delegated day-to-day responsibility for administering and interpreting the Code to a Compliance Officer. Our General Counsel has been appointed the Company's Compliance Officer under this Code.

The Company expects its directors, officers and employees to exercise reasonable judgment when conducting the Company's business. The Company encourages its directors, officers and employees to refer to this Code frequently to ensure that they are acting within both the letter and the spirit of this Code. The Company also understands that this Code will not contain the answer to every situation you may encounter or every concern you may have about conducting the Company's business ethically and legally. In these situations, or if you otherwise have questions or concerns about this Code, the Company encourages each officer and employee to speak with his or her supervisor (if applicable) or, if you are uncomfortable doing that, with the Compliance Officer under this Code.

Contents of this Code

This Code has two sections which follow this Introduction. The first section, "***Standards of Conduct***," contains the actual guidelines that our directors, officers and employees are expected to adhere to in the conduct of the Company's business. The second section, "***Compliance Procedures***," contains specific information about how this Code functions including who administers this Code, who can provide guidance under this Code and how violations may be reported, investigated and punished. This section also contains a discussion about waivers of and amendments to this Code.

A Note About Other Obligations

The Company's directors, officers and employees generally have other legal and contractual obligations to the Company. This Code is not intended to reduce or limit the other obligations that you may have to the Company. Instead, the standards in this Code should be viewed as the *minimum standards* that the Company expects from its directors, officers and employees in the conduct of the Company's business.

Standards of Conduct

Conflicts of Interest

The Company recognizes and respects the right of its directors, officers and employees to engage in outside activities which they may deem proper and desirable, provided that these activities do not impair or interfere with the performance of their duties to the Company or their ability to act in the Company's best interests. In most, if not all, cases this will mean that the Company's directors, officers and employees must avoid situations that present a potential or actual conflict between their personal interests and the Company's interests.

A "conflict of interest" occurs when a director's, officer's or employee's personal interest interferes with the Company's interests. Conflicts of interest may arise in many situations. For example, conflicts of interest can arise when a director, officer or employee takes an action or has an outside interest, responsibility or obligation that may make it difficult for him or her to perform the responsibilities of his or her position objectively and/or effectively in the Company's best interests. Conflicts of interest may also occur when a director, officer or employee or his or her immediate family member receives some personal benefit (whether improper or not) as a result of the director's, officer's or employee's position with the Company. Each individual's situation is different and in evaluating his or her own situation, a director, officer or employee will have to consider many factors.

Any material transaction or relationship that reasonably could be expected to give rise to a conflict of interest should be reported promptly to the Compliance Officer. The Compliance Officer may notify the Board or a committee thereof as he or she deems appropriate. Actual or potential conflicts of interest involving a director or executive officer other than the Compliance Officer should be disclosed directly to the Compliance Officer. Actual or potential conflicts of interest involving the Compliance Officer should be disclosed directly to the Chief Executive Officer.

Compliance with Laws, Rules and Regulations

The Company seeks to conduct its business in compliance with applicable laws, rules and regulations. No director, officer or employee shall engage in any unlawful activity in conducting the Company's business or in performing his or her day-to-day company duties, nor shall any director, officer or employee instruct others to do so.

Regulatory Compliance

The Company's business is subject to, or may in the future be subject to, a number of legal and regulatory requirements, including standards related to ethical research and development procedures, and proper scientific conduct. We expect employees to comply with all such requirements.

Protection and Proper Use of the Company's Assets

The Company's assets include its intellectual property rights and Company equipment, among other items. Loss, theft and misuse of the Company's assets has a direct impact on the

Company's business and its profitability. Employees, officers and directors are expected to protect the Company's assets that are entrusted to them and to protect the Company's assets in general. Employees, officers and directors are also expected to take steps to ensure that the Company's assets are used only for legitimate business purposes.

Corporate Opportunities

Employees, officers and directors owe a duty to the Company to advance its legitimate business interests when the opportunity to do so arises. Each employee, officer and director is prohibited from:

- diverting to himself or herself or to others any opportunities that are discovered through the use of the Company's property or information or as a result of his or her position with the Company unless such opportunity has first been presented to, and rejected by, the Company;
- using the Company's property or information or his or her position for improper personal gain; or
- competing with the Company.

Confidentiality

Confidential information generated and gathered in the Company's business plays a vital role in the Company's business, prospects and ability to compete. "Confidential information" includes all non-public information that might be of use to competitors or harmful to the Company or its customers if disclosed. Directors, officers and employees may not disclose or distribute the Company's confidential information, except when disclosure is authorized by the Company or required by applicable law, rule or regulation or pursuant to an applicable legal proceeding. Directors, officers and employees shall use confidential information solely for legitimate company purposes. Directors, officers and employees must return all of the Company's confidential and/or proprietary information in their possession to the Company when they cease to be employed by or to otherwise serve the Company.

Fair Dealing

Competing vigorously, yet lawfully, with competitors and establishing advantageous, but fair, business relationships with customers and suppliers is a part of the foundation for long-term success. However, unlawful and unethical conduct, which may lead to short-term gains, may damage a company's reputation and long-term business prospects. Accordingly, it is the Company's policy that directors, officers and employees must endeavor to deal ethically and lawfully with the Company's collaborators, customers, suppliers, competitors and employees in all business dealings on the Company's behalf. No director, officer or employee should take unfair advantage of another person in business dealings on the Company's behalf through the abuse of privileged or confidential information or through improper manipulation, concealment or misrepresentation of material facts.

Accuracy of Records

The integrity, reliability and accuracy in all material respects of the Company's books, records and financial statements is fundamental to the Company's continued and future business success. No director, officer or employee may cause the Company to enter into a transaction with the intent to document or record it in a deceptive or unlawful manner. In addition, no director, officer or employee may create any false or artificial documentation or book entry for any transaction entered into by the Company. Similarly, officers and employees who have responsibility for accounting and financial reporting matters have a responsibility to accurately record all funds, assets and transactions on the Company's books and records.

Quality of Public Disclosures

The Company is committed to providing its stockholders with complete and accurate information about its financial condition and results of operations as required by the securities laws of the United States. It is the Company's policy that the reports and documents it files with or submits to the Securities and Exchange Commission, and its earnings releases and similar public communications made by the Company, include full, fair, accurate, timely and understandable disclosure. Officers and employees who are responsible for these filings and disclosures, including the Company's principal executive, financial and accounting officers, must use reasonable judgment and perform their responsibilities honestly, ethically and objectively in order to ensure that this disclosure policy is fulfilled. The Company's senior management are primarily responsible for monitoring the Company's public disclosure.

Political Contributions/Gifts

Business contributions to political campaigns are strictly regulated by federal, state, provincial and local law in the United States, Canada and other jurisdictions. Accordingly, all political contributions proposed to be made with the Company's funds must be coordinated through and approved by the Compliance Officer. Directors, officers and employees may not, without the approval of the Compliance Officer, use any of the Company's funds for political contributions of any kind to any political candidate or holder of any national, state, provincial or local government office. Directors, officers and employees may make personal contributions, but should not represent that he or she is making any such contribution on the Company's behalf. Similar restrictions on political contributions may apply in other countries. Specific questions should be directed to the Compliance Officer.

Bribes, Kickbacks and Other Improper Payments

The Company does not permit or condone bribes, kickbacks or other improper payments, transfers or receipts. No director, officer or employee should offer, give, solicit or receive any money or other item of value for the purpose of obtaining, retaining or directing business or bestowing or receiving any kind of favored treatment. In particular, the U.S. Foreign Corrupt Practices Act ("FCPA") prohibits any U.S. individual or business from authorizing, offering or paying money or anything of value, directly or indirectly, to any foreign official or employee, political party, or candidate for public office for the purpose of obtaining or maintaining business

or for any other business advantage. Violation of the FCPA could subject the Company and its individual directors, officers and employees to serious fines and criminal penalties.

International Trade Controls

Many countries regulate international trade transactions, such as imports, exports and international financial transactions. In addition, the United States prohibits any cooperation with boycotts against countries friendly to the United States or against firms that may be "blacklisted" by certain groups or countries. It is the Company's policy to comply with these laws and regulations even if it may result in the loss of some business opportunities. Employees should learn and understand the extent to which U.S. and international trade controls apply to transactions conducted by the Company.

Compliance Procedures

Communication of Code

All directors, officers and employees will be supplied with a copy of the Code upon the later of the Board's adoption of the Code or beginning service at the Company. Updates of the Code will be provided from time to time. A copy of the Code is also available to all directors, officers and employees by requesting one from the human resources department or by accessing the Company's website at www.atyrpharma.com.

Monitoring Compliance and Disciplinary Action

The Company's management, under the supervision of its Board or a committee thereof or, in the case of accounting, internal accounting controls, auditing or securities law matters, the Audit Committee of the Board of Directors (the "Audit Committee"), shall take reasonable steps from time to time to (i) monitor compliance with the Code, and (ii) when appropriate, impose and enforce appropriate disciplinary measures for violations of the Code.

Disciplinary measures for violations of the Code will be determined in the Company's sole discretion and may include, but are not limited to, counseling, oral or written reprimands, warnings, probation or suspension with or without pay, demotions, reductions in salary, termination of employment or service, and restitution.

The Company's management shall periodically report to the Board or a committee thereof on these compliance efforts including, without limitation, periodic reporting of alleged violations of the Code and the actions taken with respect to any such violation.

Reporting Concerns/Receiving Advice

Communication Channels

Be Proactive. Every employee is encouraged to act proactively by asking questions, seeking guidance and reporting suspected violations of the Code and other policies and procedures of the Company, as well as any violation or suspected violation of applicable law, rule or regulation arising in the conduct of the Company's business or occurring on the Company's property. **If any**

employee believes that actions have taken place, may be taking place, or may be about to take place that violate or would violate the Code or any law, rule or regulation applicable to the Company, he or she is obligated to bring the matter to the attention of the Company.

Seeking Guidance. The best starting point for an officer or employee seeking advice on ethics-related issues or reporting potential violations of the Code will usually be his or her supervisor. However, if the conduct in question involves his or her supervisor, if the employee has reported the conduct in question to his or her supervisor and does not believe that he or she has dealt with it properly, or if the officer or employee does not feel that he or she can discuss the matter with his or her supervisor, the employee may raise the matter with the Compliance Officer.

Our whistleblower hotline number is 1-855-405-6642. There is also an online reporting option: http://atyrpharma.ethicspoint.com.

Communication Alternatives. Any officer or employee may communicate with the Compliance Officer, or report potential violations of the Code, by any of the following methods:

- By e-mail to ndenyes@atyrpharma.com (anonymity cannot be maintained);
- In writing (which may be done anonymously as set forth below under "Anonymity"), addressed to the Compliance Officer, by U.S. mail to c/o aTyr Pharma, Inc., 3545 John Hopkins Court, Suite #250, San Diego, CA 92121; or
- Online at http://atyrpharma.ethicspoint.com (which may be done anonymously as set forth below under "Anonymity").

Reporting Accounting and Similar Concerns. Any concerns or questions regarding any potential violations of the Code, any company policy or procedure or applicable law, rules or regulations that involves accounting, internal accounting controls, auditing or securities law (including FCPA) matters will be directed to the Audit Committee or a designee of the Audit Committee in accordance with the procedures established by the Audit Committee for the receipt, retention and treatment of complaints regarding accounting, internal accounting controls or auditing matters. Officers and employees may also communicate directly with the Audit Committee or its designee regarding such matters by the following methods (which may be done anonymously as set forth below under "Anonymity"):

- By e-mail to auditcommitteechair@atyrpharma.com (anonymity cannot be maintained);
- In writing (which may be done anonymously as set forth below under "Anonymity"), addressed to the Chairperson of the Audit Committee, by U.S. mail to c/o aTyr Pharma, Inc., 3545 John Hopkins Court, Suite #250, San Diego, CA 92121; or
- Online at http://atyrpharma.ethicspoint.com (which may be done anonymously as set forth below under "Anonymity").

Cooperation. Employees are expected to cooperate with the Company in any investigation of a potential violation of the Code, any other company policy or procedure, or any applicable law, rule or regulation.

Misuse of Reporting Channels. Employees must not use these reporting channels in bad faith or in a false or frivolous manner or to report grievances that do not involve the Code or other ethics-related issues.

Director Communications. In addition to the foregoing methods, a director may also communicate concerns or seek advice with respect to this Code by contacting the Board through its Chairperson or the Audit Committee.

Anonymity

When reporting suspected violations of the Code, the Company prefers that officers and employees identify themselves to facilitate the Company's ability to take appropriate steps to address the report, including conducting any appropriate investigation. However, the Company also recognizes that some people may feel more comfortable reporting a suspected violation anonymously.

If an officer or employee wishes to remain anonymous, he or she may do so, and the Company will use reasonable efforts to protect the confidentiality of the reporting person subject to applicable law, rule or regulation or to any applicable legal proceedings. In the event the report is made anonymously, however, the Company may not have sufficient information to look into or otherwise investigate or evaluate the allegations. Accordingly, persons who make reports anonymously should provide as much detail as is reasonably necessary to permit the Company to evaluate the matter(s) set forth in the anonymous report and, if appropriate, commence and conduct an appropriate investigation.

No Retaliation

The Company expressly forbids any retaliation against any officer or employee who, acting in good faith on the basis of a reasonable belief, reports suspected misconduct. Specifically, the Company will not discharge, demote, suspend, threaten, harass or in any other manner discriminate against, such an officer or employee in the terms and conditions of his or her employment. Any person who participates in any such retaliation is subject to disciplinary action, including termination.

Waivers and Amendments

No waiver of any provisions of the Code for the benefit of a director or an executive officer (which includes without limitation, for purposes of this Code, the Company's principal executive, financial and accounting officers) shall be effective unless (i) approved by the Board or, if permitted by the rules of The Nasdaq Stock Market, the Audit Committee, and (ii) if applicable, such waiver is promptly disclosed to the Company's stockholders in accordance with applicable U.S. securities laws and/or the rules and regulations of the exchange or system on which the Company's shares are traded or quoted, as the case may be.

Any waivers of the Code for other employees may be made by the Compliance Officer, the Board or, if permitted, the Audit Committee.

All amendments to the Code must be approved by the Board or the Audit Committee and, if applicable, must be promptly disclosed to the Company's stockholders in accordance with applicable U.S. securities laws and the rules of The Nasdaq Stock Market as the case may be.

ADOPTED: April 25, 2015
EFFECTIVE: May 6, 2015
AMENDED: February 5, 2020

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the following Registration Statements:

(1) Registration Statement (Form S-1 No. 333-248905) of aTyr Pharma, Inc.,

(2) Registration Statements (Form S-3 Nos. 333-220463, 333-250095, 333-258725 and 333-259571) of aTyr Pharma, Inc.,

(3) Registration Statement (Form S-8 No. 333-203955) pertaining to the ATYR PHARMA, INC. 2014 STOCK PLAN, the ATYR PHARMA, INC. 2015 STOCK OPTION AND INCENTIVE PLAN, and the ATYR PHARMA, INC. 2015 EMPLOYEE STOCK PURCHASE PLAN,

(4) Registration Statements (Form S-8 Nos. 333-210543 and 333-223865) pertaining to the ATYR PHARMA, INC. 2015 STOCK OPTION AND INCENTIVE PLAN, and the ATYR PHARMA, INC. 2015 EMPLOYEE STOCK PURCHASE PLAN,

(5) Registration Statements (Form S-8 Nos. 333-216880 and 333-231594) pertaining to the ATYR PHARMA, INC. 2015 STOCK OPTION AND INCENTIVE PLAN, the ATYR PHARMA, INC. 2015 EMPLOYEE STOCK PURCHASE PLAN, and NON-QUALIFIED STOCK OPTION INDUCEMENT AWARDS, and

(6) Registration Statement (Form S-8 Nos. 333-248090 and 333-256145) pertaining to the ATYR PHARMA, INC. 2015 STOCK OPTION AND INCENTIVE PLAN, AS AMENDED

of our report dated March 15, 2022, with respect to the consolidated financial statements of aTyr Pharma, Inc. included in this Annual Report (Form 10-K) of aTyr Pharma, Inc. for the year ended December 31, 2021.

/s/ Ernst & Young LLP

San Diego, California

March 15, 2022

Exhibit 31.1

CERTIFICATION PURSUANT TO
RULE 13a-14(a) AND 15d-14(a) OF THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Sanjay S. Shukla, certify that:

1. I have reviewed this Annual Report on Form 10-K of aTyr Pharma, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

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

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

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

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

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

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

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

Date: March 15, 2022

/s/ Sanjay S. Shukla
Sanjay S. Shukla, M.D., M.S.
President, Chief Executive Officer and Director
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION PURSUANT TO
RULE 13a-14(a) AND 15d-14(a) OF THE SECURITIES EXCHANGE ACT 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Jill M. Broadfoot, certify that:

1. I have reviewed this Annual Report on Form 10-K of aTyr Pharma, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

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

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

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

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

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

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

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

Date: March 15, 2022

/s/ Jill M. Broadfoot
Jill M. Broadfoot
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 aTyr Pharma, Inc. (the "Company") for the year ended December 31, 2021, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Sanjay S. Shukla, President and Chief Executive Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 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, as amended ("the Exchange Act"); and

2. The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 15, 2022

/s/ Sanjay S. Shukla

Sanjay S. Shukla, M.D., M.S.
President, Chief Executive Officer and Director
(Principal Executive Officer)

The foregoing certification is being furnished solely to accompany the Report pursuant to 18 U.S.C. Section 1350, is not being filed for purposes of Section 18 of the Exchange Act, 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 of the Sarbanes-Oxley Act of 2002 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 aTyr Pharma, Inc. (the "Company") for the year ended December 31, 2021, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Jill M. Broadfoot, Chief Financial Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 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, as amended (the "Exchange Act"); and

2. The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 15, 2022

/s/ Jill M. Broadfoot
Jill M. Broadfoot
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. Section 1350, and is not being filed for purposes of Section 18 of the Exchange Act, 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 of the Sarbanes-Oxley Actor of 2002 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.