

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

**Form 10-K**

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

For the fiscal year ended December 31, 2022

☐ **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 001-39202

**Annovis Bio, Inc.**

(Exact name of registrant as specified in its charter)

Delaware  
(State or other jurisdiction of  
incorporation or organization)

26-2540421  
(I.R.S. Employer  
Identification No.)

1055 Westlakes Drive, Suite 300  
Berwyn, PA 19312

(Address of principal executive offices including zip code)

(610) 727-3913

(Registrant's telephone number, including area code)

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 \$0.0001 per share	ANVS	New York Stock Exchange

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 Section 15(d) of the Exchange Act. Yes ☐ No ☒

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

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

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

Large accelerated filer ☐

Accelerated filer ☐

Non-accelerated filer ☒

Smaller reporting company ☐

Emerging growth company ☒

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

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

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

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

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

As of June 30, 2022, the last business day of the registrant's most recently completed second fiscal quarter, the aggregate market value of the registrant's common stock held by non-affiliates of the registrant was \$63,483,880 based on the closing sale price as reported on the NYSE.

The number of shares of the issuer's common stock outstanding as of March 30, 2023, was 8,216,678.

**Documents Incorporated by Reference**

Certain portions, as expressly described in this report, of the registrant's proxy statement for the 2023 Annual Meeting of the Stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K.

## TABLE OF CONTENTS

	<b><u>Page</u></b>
Cautionary Note Regarding Forward-Looking Statements. ....	3
Summary of Risk Factors. ....	4
<b>Part I.</b> ....	6
Item 1. Business. ....	6
Item 1A. Risk Factors. ....	32
Item 1B. Unresolved Staff Comments. ....	80
Item 2. Properties. ....	80
Item 3. Legal Proceedings. ....	80
Item 4. Mine Safety Disclosures. ....	80
<b>Part II.</b> ....	81
Item 5. Market for Registrant’s Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities. ...	81
Item 7. Management’s Discussion and Analysis of Financial Condition and Results of Operations. ....	81
Item 7A. Quantitative and Qualitative Disclosures About Market Risk. ....	90
Item 8. Financial Statements and Supplementary Data. ....	90
Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure. ....	90
Item 9A. Controls and Procedures. ....	90
Item 9B. Other Information. ....	91
<b>Part III.</b> ....	91
Item 10. Directors, Executive Officers and Corporate Governance. ....	91
Item 11. Executive Compensation. ....	91
Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters. ....	92
Item 13. Certain Relationships and Related Transactions and Director Independence. ....	92
Item 14. Principal Accountants Fees and Services. ....	92
<b>Part IV.</b> ....	92
Item 15. Exhibits and Financial Statement Schedules. ....	92
Item 16. Form 10-K Summary. ....	94
Index to Financial Statements. ....	F-1
Signatures	

## **Explanatory Note**

### ***Restatement of Previously Issued Quarterly Financial Statements***

During the preparation of our 2022 audited combined financial statements and notes thereto, we concluded that there were material research and development expenses and related balance sheet errors in our previously issued unaudited condensed financial statements as of and for each of the quarterly and year to date periods ended March 31, 2022, June 30, 2022 and September 30, 2022, primarily relating to the timing of payments for research and development expenses and recognition of expenses. As a result of such errors, we concluded that each of the issued 2022 unaudited condensed financial statements were materially misstated, and have restated herein our previously issued unaudited condensed financial statements for each of the quarterly and year to date periods ended March 31, 2022, June 30, 2022, and September 30, 2022. The restatement corrections impact certain components within operating cash flows of the unaudited condensed statements of cash flows. Total operating cash flows, investing activities, financing activities, and cash and cash equivalents are unchanged as a result of the restatements and as a result are not restated herein.

In this Annual Report on Form 10-K for the year ended December 31, 2022, we are restating (the “Restatement”) our previously issued (i) unaudited condensed balance sheets as of March 31, 2022, June 30, 2022 and September 30, 2022, (ii) unaudited condensed statements of operations and comprehensive loss for the three months ended March 31, 2022, three and six months ended June 30, 2022, and three and nine months ended September 30, 2022, (iii) unaudited condensed statements of cash flows for the three months ended March 31, 2022, six months ended June 30, 2022 and nine months ended September 30, 2022, in each of the Quarterly Reports on Form 10-Q for the quarterly periods ended March 31, 2022, June 30, 2022 and September 30, 2022 (the “Prior Quarterly Financial Statements”).

The financial information that was previously filed or otherwise reported for the Prior Quarterly Financial Statements is superseded by the information in this Annual Report on Form 10-K, Note 12 - Restatement of Previously Issued Unaudited Condensed Financial Statements. We have not filed and do not intend to file amendments to our Quarterly Reports on Form 10-Q for any of the quarterly periods in fiscal year 2022. Accordingly, investors should rely only on the restated Financial Statements and related disclosures included in this 2022 Form 10-K for the applicable periods or in future filings with the SEC (as applicable), and not on any previously issued or filed reports, earnings releases or similar communications including the Financial Statements.

### **Internal Control Considerations**

In connection with the Restatement described above, management has determined that there was a material weakness in the Company's operation of effective internal control over financial reporting related to its application of ASC 606 for collaboration and license agreements as of December 31, 2022. For a discussion of management's considerations of the Company's disclosures controls and procedures, internal controls over financial reporting, and the material weakness identified, refer to “Controls and Procedures” in Part II, Item 9A.

## Cautionary Note Regarding Forward-Looking Statements.

This Annual Report on Form 10-K contains forward-looking statements, within the meaning of the U.S. Private Securities Litigation Reform Act of 1995, that involve substantial risks and uncertainties. In some cases, you can identify forward-looking statements by the words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “might,” “objective,” “ongoing,” “plan,” “predict,” “project,” “potential,” “should,” “will,” or “would,” and or the negative of these terms, or other comparable terminology intended to identify statements about the future. These statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. Although we believe that we have a reasonable basis for each forward-looking statement contained in this Annual Report on Form 10-K, we caution you that these statements are based on a combination of facts and factors currently known by us and our expectations of the future, about which we cannot be certain.

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

- our cash and cash equivalents balance, runway and needs as well as financing plans;
- the timing of regulatory submissions;
- our ability to obtain and maintain regulatory approval of our existing product candidates and any other product candidates we may develop, and the labeling under any approval we may obtain;
- our business strategies;
- risks relating to the timing and costs of clinical trials and the timing and costs of other expenses;
- risks related to market acceptance of products;
- risks associated with our reliance on third-party organizations;
- our competitive position;
- assumptions regarding the size of the available market, product pricing and timing of commercialization of our product candidates;
- our intellectual property position and our ability to maintain and protect our intellectual property rights;
- our results of operations, financial condition, liquidity, prospects, and growth strategies;
- the industry in which we operate; and
- the trends that may affect the industry or us.

You should refer to Part I, Item 1A “Risk Factors” of this Annual Report on Form 10-K for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. As a result of the risks, uncertainties and assumptions described under “Risk Factors” and elsewhere, we cannot assure you that the forward-looking statements in this Annual Report on Form 10-K will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame or at all.

You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee that the future results, levels of activity,

performance, or events and circumstances reflected in the forward-looking statements will be achieved or occur. We undertake no obligation to update publicly any forward-looking statements for any reason after the date of this report to conform these statements to new information, actual results or changes in our expectations, except as required by law.

### **Summary of Risk Factors.**

The following is a summary of the principal risks described below in Part I, Item 1A “Risk Factors” in this Annual Report on Form 10-K. We believe that the risks described in the “Risk Factors” section are material to investors, but other factors not presently known to us or that we currently believe are immaterial may also adversely affect us. The following summary should not be considered an exhaustive summary of the material risks facing us, and it should be read in conjunction with the “Risk Factors” section and the other information contained in this Annual Report on Form 10-K .

- Because our auditor has issued a going concern opinion regarding our company, there is an increased risk associated with an investment in our company.
- We have incurred significant net losses since inception and anticipate that we will continue to incur net losses for the foreseeable future and may never achieve or maintain profitability.
- We will require substantial additional capital to fund our operations, and if we fail to obtain necessary funding, we may not be able to complete the development and commercialization of our product candidates.
- We have limited operating history and no history of commercializing pharmaceutical products.
- Unstable market and economic conditions may have serious adverse consequences on our business, financial condition and stock price.
- We are heavily dependent on the success of Buntanetap, our most advanced product candidate, which is still under clinical development, and if this drug does not receive regulatory approval or is not successfully commercialized, our business will be materially harmed.
- We have concentrated our research and development efforts on the treatment of Alzheimer’s disease (“AD”) and Parkinson’s disease (“PD”), diseases that have seen limited success in drug development. Further, Buntanetap is based on a new approach to treating AD and PD, which makes it difficult to predict the time and cost of development and subsequent obtaining of regulatory approval.
- If we are not successful in discovering, developing, and commercializing additional product candidates, our ability to expand our business and achieve our strategic objectives would be impaired.
- Clinical trials, including the enrollment and retention of patients, are expensive, time-consuming, difficult to design and implement, and involve an uncertain outcome.
- The regulatory approval processes of the FDA and comparable foreign authorities are lengthy, time consuming and inherently unpredictable, and if we are ultimately unable to obtain regulatory approval for Buntanetap or any other product candidates, our business will be substantially harmed.
- Results of preclinical studies, early clinical trials or analyses may not be indicative of results obtained in later trials. 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 further subject to audit and verification procedures that could result in material changes in the final data. Furthermore, undue reliance on interim analyses may be detrimental to our long-term clinical development plans, which could harm our business, operating results, prospects or financial condition.
- Our product candidates may cause serious adverse events or undesirable side effects, which may delay or prevent marketing approval, or, if approved, require them to be taken off the market, require them to include safety warnings or otherwise limit their sales.

- The market opportunities for Buntanetap or any other product candidates, if approved, may be smaller than we anticipate, which could adversely affect our business, financial condition and results of operations.
- Even if we obtain regulatory approval for Buntanetap or any product candidates, we will still face extensive and ongoing regulatory requirements and obligations.
- We face significant competition from other biotechnology and pharmaceutical companies and our operating results will suffer if we fail to compete effectively.
- The successful commercialization of Buntanetap and any other product candidates we develop will depend in part on market acceptance; the extent to which governmental authorities and health insurers establish adequate coverage, reimbursement levels, and pricing policies; and our sales, marketing and distribution capabilities.
- A variety of risks associated with operating internationally could materially adversely affect our business.
- We currently rely on third parties for the production of clinical supply of Buntanetap and for the conduct, supervision and monitoring of our clinical trials. If those third parties do not successfully carry out their contractual duties, or if they perform in an unsatisfactory manner or do not comply with regulatory standards and requirements, it may harm our business.
- Changes in methods of product candidate manufacturing or formulation may result in additional cost or delay.
- Enacted and future healthcare and other legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates, if approved, increase the liabilities to which we may become subject, and affect the prices we may set or the manner in which we conduct and plan to conduct our business.
- If we are unable to obtain, maintain and enforce patent or other intellectual property protection for Buntanetap or any future product candidates or technology or if the scope of the patent protection obtained is not sufficiently broad, our competitors or other third parties could develop and commercialize products similar or identical to ours, our ability to successfully commercialize Buntanetap or any future product candidates may be adversely affected and we may not be able to compete effectively in our markets.
- We may be subject to claims challenging the inventorship of our patents and other intellectual property. We may additionally become subject to third parties' claims alleging infringement of their patents and proprietary rights, or we may need to become involved in lawsuits to protect or enforce our patents, which could be costly, time consuming, delay or prevent the development and commercialization of our product candidates or put our patents and other proprietary rights at risk.
- The cash and cash equivalents that we use to meet our working capital and operating expense needs are held in deposit accounts at two financial institutions. If one or both financial institutions fail, our deposit accounts could be adversely affected due to the loss of or delay in obtaining access to all or a portion of our uninsured funds.
- The market price of our common stock has been volatile and fluctuated substantially in the past, and may continue to experience volatility and substantial fluctuations in the future, which could result in substantial losses for purchasers of our common stock.
- We have been subject to securities class action litigation in the past, and could be subject to such litigation in the future.
- We identified a material weakness in our internal control over financial reporting, which resulted in the restatement of our financial statements for several prior quarterly and year-to-date periods. If remediation of this material weakness is not effective, or if we fail to maintain an effective system of internal control over financial reporting in the future, we may not be able to accurately or timely report our financial condition or operating results, which may adversely affect investor confidence in our company and, as a result, the value of our common stock.
- The restatement of our prior quarterly financial statements may affect investor confidence and raise reputational issues and may subject us to additional risks and uncertainties, including increased professional costs and the increased possibility of legal proceedings and regulatory inquiries.

## PART I

### Item 1. Business.

#### Our Company

Annovis Bio, Inc. is a clinical stage, drug platform company addressing neurodegeneration, such as Alzheimer's disease ("AD") and Parkinson's disease ("PD"). We are developing our lead product candidate, Buntanetap, which is designed to address AD, PD, and potentially other chronic neurodegenerative diseases. Buntanetap is a synthetically produced small molecule, orally administered, brain penetrant compound. In several studies, Buntanetap was observed to inhibit the synthesis of neurotoxic proteins—APP/A $\beta$  ("APP"), tau/phospho-tau ("tau") and  $\alpha$ -Synuclein (" $\alpha$ SYN")—that are one of the main causes of neurodegeneration. High levels of neurotoxic proteins lead to impaired axonal transport, which is responsible for the communication between and within nerve cells. When that communication is impaired, the immune system is activated and attacks the nerve cells, eventually killing them. We have observed in our clinical studies in early AD and early PD patients and pre-clinical studies in mice and rats that Buntanetap lowered neurotoxic protein levels leading to improved axonal transport, reduced inflammation, lower nerve cell death and improved affected function.

In 2021, we completed two Phase 1/2 clinical studies: one in 14 early AD patients, and one in 54 early PD patients (together, the "AD/PD Trials"). In the AD/PD Trials, early AD patients were defined as those with a Mini Mental State Examination (MMSE) score between 19 and 28 and early PD patients as those patients at Hoehn & Yahr stages 1, 2 or 3. MMSE is a brief screening instrument used to assess cognitive function, with total scores ranging from 0 to 30 and a lower score indicating greater disease severity, while the Hoehn & Yahr scale is a medical assessment used to measure staging of the functional disability associated with PD where a higher stage indicates greater disease severity. In collaboration with the Alzheimer's Disease Cooperative Study ("ADCS"), we also conducted a trial in 16 early AD patients (the "ADCS Trial"). In the ADCS Trial, early AD patients were defined as those patients with a MMSE score between 19 and 28. All three clinical trials were double-blind, placebo-controlled studies. We designed the studies by applying our understanding of the underlying neurodegenerative disease states, and measured both target and pathway validation in the spinal fluid of patients to determine whether patients improved following treatment. In addition to meeting their primary endpoints of safety and tolerability and secondary endpoint of pharmacokinetics of Buntanetap, our AD/PD Trials met exploratory endpoints of measures of biomarkers and improvements in cognition in AD patients, and in function in PD patients. We believe that the AD/PD Trials represent the first double-blind placebo-controlled studies that showed improvements in AD patients, as measured by ADAS-Cog, and in PD patients, as measured by UPDRS. Following completion of the AD/PD Trials, we submitted our data to the U.S. Food and Drug Administration ("FDA") and requested direction to further pursue the development of Buntanetap in early PD patients. With the FDA's guidance, we initiated a Phase 3 study in early PD patients in August 2022 (our "Phase 3 PD Study"). In the Phase 3 PD Study, early PD patients were defined as those at Hoehn & Yahr stages 1, 2 or 3 and OFF times of less than two hours per day. OFF time refers to when PD motor and/or non-motor symptoms occur between medication doses. We also submitted a proposed protocol for the treatment of moderate AD to the FDA, and after receiving permission to proceed, we initiated a Phase 2/3 study in mild to moderate AD patients in February 2023 (our "Phase 2/3 AD Study"). In the Phase 2/3 AD Study, mild to moderate AD patients were defined as those with a MMSE score between 14 and 24. At the completion of the ADCS Trial, the data showed that Buntanetap is a translational inhibitor in humans just like in animals, and we further observed that there was statistical improvement in cognition in early AD patients, just like in the AD/PD Trials.

Our Phase 3 PD Study and Phase 2/3 AD Study each have built in interim analyses. Our Phase 3 PD Study incorporated an interim analysis at two months, the results of which were disclosed on March 31, 2023. The pre-planned interim analysis was conducted by our data analytics provider based on 132 patients from all cohorts collectively for which baseline and two-month data was available. As the interim analysis was conducted at two months of the six-month endpoint and only on 132 patients, it may not be indicative of the results at six months for the full patient population because as the trial progresses, clinical outcomes may materially change as patient enrollment continues and more patient data become available, or different conclusions or considerations may qualify such results once additional data have been received and fully evaluated. Based on the results of the interim analysis, we intend to proceed with the Phase 3 PD Study as planned in accordance with the previously established protocol. We remain blinded to the Phase 3 PD Study and we do not have safety or efficacy data from the trial. A separate safety interim analysis is in process and we expect that interim analysis to be released in the second quarter of 2023. We intend to disclose the results of an interim analysis for our Phase 2/3 AD Study in Fall 2023. We plan to consult with the FDA following completion of these interim analyses, to obtain feedback on our ongoing and planned AD and PD studies, including conducting an open label extension study following the completion of the initial trials. Using the data from the Phase 3 PD Study interim analysis, we intend to design an 18-month long disease-modifying Phase 3 study in the same early PD patients. In addition, we intend to conduct a short 6-month study in advanced PD patients during the second half of the 18-month disease modifying Phase 3 study, at which time we will define the advanced PD patient population for

the purposes of such study. Similarly, using the data from the Phase 2/3 AD Study interim analysis, we intend to design an 18-month disease modifying Phase 3 study in the same early AD patient population. In addition, we intend to conduct a short 6-month study in advanced AD patients during the second half of the 18-month disease modifying Phase 3 study, at which time we will define the advanced AD patient population for the purposes of such study. We expect both the ongoing Phase 3 PD Study and the Phase 2/3 AD Study to be completed by the end of 2023, and we intend to announce the data from the final analyses in the first quarter of 2024.

By the end of 2026, our goal is to have conducted the required pivotal studies for Buntanetap to be able to file two new drug applications (“NDAs”) with the FDA.

We believe that we are the only company developing a drug for AD and PD that is designed to inhibit more than one neurotoxic protein, and has a mechanism of action designed to restore nerve cell axonal and synaptic activity. By improving brain function, our goal is to treat memory loss and dementia associated with AD as well as body and brain function associated with PD. Based on pre-clinical and clinical data collected to date, we believe that Buntanetap has the potential to be the first drug to interfere with the underlying mechanism of neurodegeneration, potentially enabling Buntanetap to be the only drug to improve cognition in AD and motor function in PD. The industry has encountered challenges in specifically targeting one neurotoxic protein, be it APP, tau or  $\alpha$ SYN, indicating that doing so does not change the course of neurodegeneration. Our goal is to develop a disease modifying drug (“DMD”) for patients with neurodegeneration by leveraging our clinical and pre-clinical data to inhibit the three most relevant neurotoxic proteins. Studies have found that AD and PD are the most common neurodegenerative diseases in the U.S., and accordingly these diseases present two unmet needs of the aging population and two potentially large U.S. markets if a DMD is developed and approved.

Our leadership team has substantial experience and extensive industry knowledge, and has been successful with respect to meeting clinical timelines, enrollment progression and data readouts. Maria L. Maccicchini, our Founder, President and CEO, founded Annovis in May 2008 to develop better therapeutics for neurodegeneration. She was previously the Founder and CEO of Symphony Pharmaceuticals/Annovis, a biotech company that sold to Transgenomic in 2001. She was also the General Manager of Bachem Bioscience, the U.S. subsidiary of Bachem AG, Switzerland. Dr. Maccicchini did one postdoc at Caltech and one at the Roche Institute of Immunology. Her PhD in biochemistry is from the Biocenter of Basel with a two-year visiting fellowship at The Rockefeller University. Henry Hagopian, our Chief Financial Officer, has over 30 years of experience in corporate finance, accounting, treasury and capital raising in both public and private companies. Prior to joining Annovis, Mr. Hagopian was Senior Vice President, Finance and Treasurer at Organogenesis, where he assisted in raising several rounds of capital in excess of \$310 million. He spent 15 years in positions at AT&T, Lucent Technologies and CIRCOR International, Inc. Mr. Hagopian holds an M.B.A. and M.S. from the Carroll Graduate School of Management at Boston College. Cheng Fang, Senior Vice President, Research and Development, has broad scientific knowledge and over a decade of experience working in the field of neurodegenerative diseases. She previously worked at Clarivate Analytics and the Cornell Institute for Medical Research. As a Research Assistant Professor at Boston University, she designed projects on prion disease and AD. She has a PhD in biology and neuroscience from Pennsylvania State University. She also holds a B.S. in biopharmaceutics from Nanjing University. Eve Damiano, Senior Vice President, Regulatory, has spent over 35 years in the biotechnology sector, focusing on the definition and execution of regulatory strategies. Ms. Damiano has held various senior management positions throughout her career, with experience garnered at companies including Centocor, MedImmune, OraSure Technologies and Vicuron Pharmaceuticals. Ms. Damiano holds a track record in the definition and execution of regulatory strategies. She holds an M.S. from the Drexel University College of Medicine. Melissa Gaines, Vice President, Clinical Operations, is an accomplished clinical research professional with over 20 years’ experience garnered from positions held in academia, contract research organizations and pharmaceutical companies. She was previously Senior Director, Clinical Operations, for Worldwide Clinical Trials, and has over a decade of experience at INC Research. She has demonstrated proven success in leading cross-functional teams as well as driving operational success. She holds a B.A. in Psychology from Millersville University of Pennsylvania.

## **Mechanism of Action**

Our lead product candidate, Buntanetap, is designed as an oral translational inhibitor of neurotoxic aggregating proteins (“TINAP”) such as APP, tau and  $\alpha$ SYN. To understand how Buntanetap can potentially inhibit translation, we undertook two complementary approaches: a macro approach to examine all proteins in the cell whose translation is affected by Buntanetap, and a micro approach to study the mechanism of action using molecular biology, to understand and validate the binding and function.



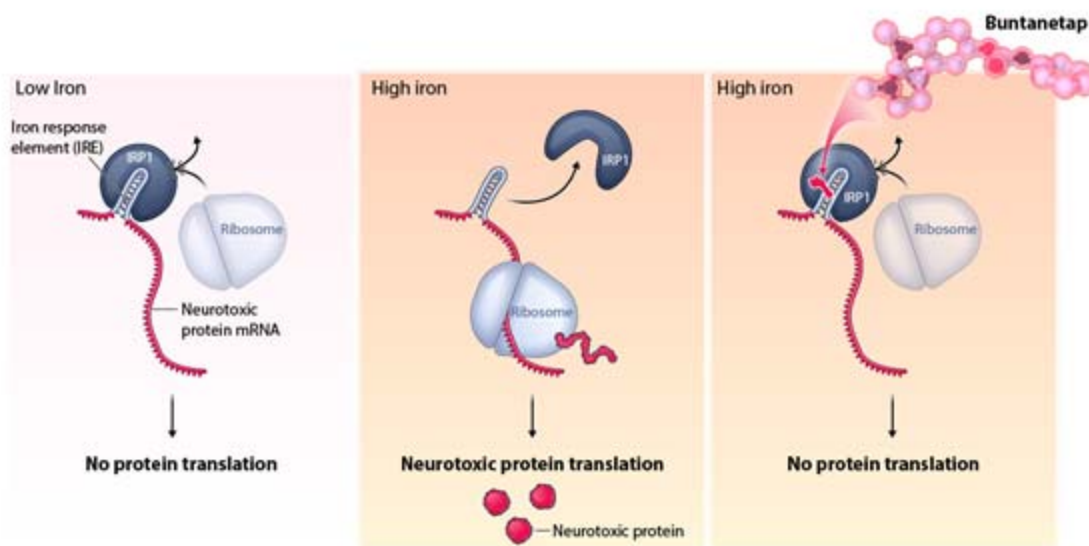
First, the non-biased proteomics approach was applied to explore what proteins in the total protein universe were specifically downregulated by Buntanetap. We have observed that, in addition to the proteins already known to be reduced by Buntanetap, other neurotoxic aggregating proteins - huntingtin protein (“HTT”) and TDP43 - were downregulated as well.

A detailed analysis of the reduction of these protein levels was conducted in five different laboratories using multiple methodologies. The results observed in the analysis revealed that the mRNAs of these proteins have a special region, an atypical stem loop, that is preserved and responsible for their translation. When this region is bound to an RNA binding protein, the mRNA is not translated. When this region is free, the mRNA is translated. In neurodegenerative conditions, the mRNA coding for these neurotoxic proteins is over-translated, produces high levels of these proteins and causes them to become toxic. Buntanetap was observed to specifically increase the affinity between this special region and the RNA binding protein, thereby showing the potential to prevent the mRNA from being released and translated.

This leads to lower translation, lower levels of neurotoxic proteins, and less toxicity in the brain. By preventing the overexpression of these neurotoxic proteins, Buntanetap is designed to reverse the downstream toxic cascade that leads to neurodegeneration and reinstates homeostasis.

This rigorous approach to understanding the mode of action shows that while Buntanetap does lower the levels of more than one neurotoxic protein, it is exquisitely specific for the atypical stem loops in the mRNAs of these proteins.

The following illustration shows the mechanism of action of Buntanetap:



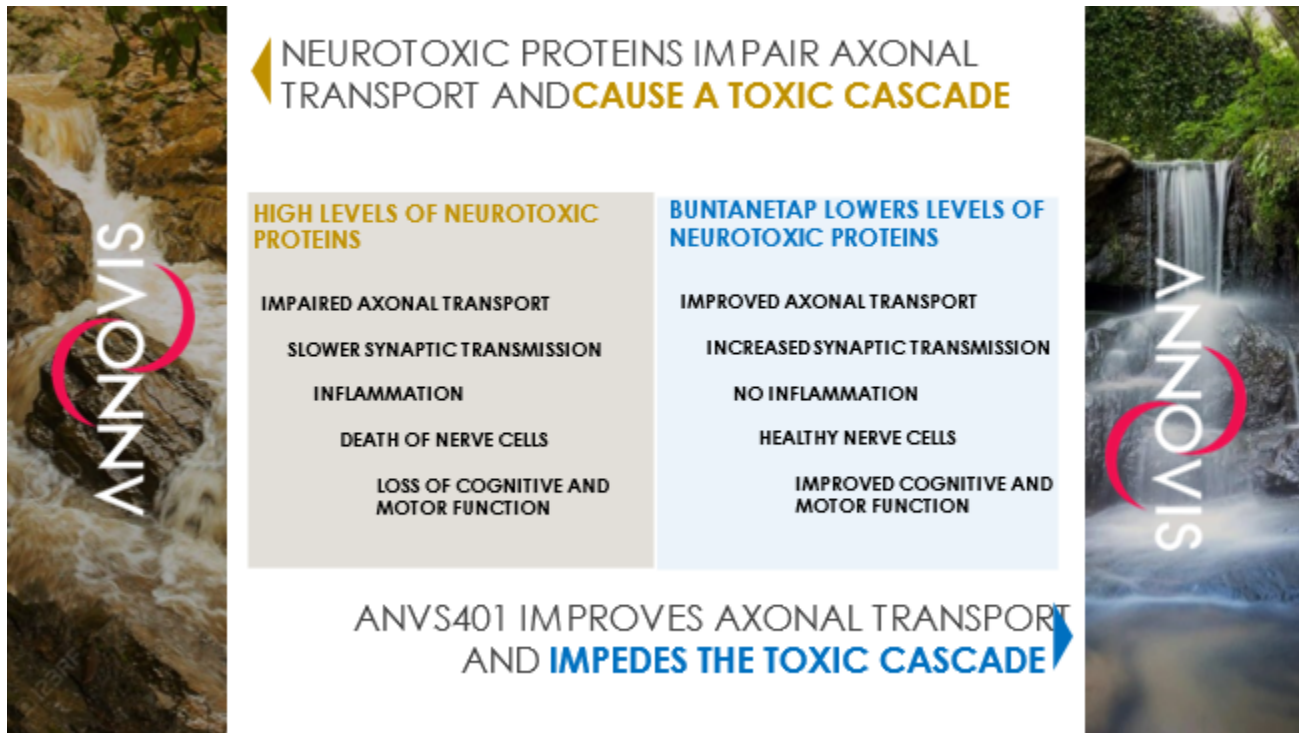
MOA; Chen XQ et al. Pharmaceutics 09-2021 Iron and Neurodegeneration; Wong f. et al. Frontiers Aging Neuroscience; 03-2022

The special region in the mRNA is a 5'UTR iron responsive element (“IRE”) present in all mRNAs of neurotoxic aggregating proteins. The RNA binding protein is the Iron Regulatory Protein -1 (“IRP1”) that specifically binds the IREs of neurotoxic aggregating proteins.

### The Toxic Cascade Leading to Nerve Cell Death and Loss of Function

The toxic cascade in neurodegeneration begins with high levels of neurotoxic proteins which lead to impaired axonal transport, inflammation, death of nerve cells and loss of cognition and motor function. Buntanetap and ANVS405, our product candidates designed to treat acute neurodegeneration, including traumatic brain injury (“TBI”), have a mechanism of action we

believe to be unique. The mechanism of action is designed to inhibit the over-translation of and reduce the levels of APP, tau and  $\alpha$ SYN, which play a central role in the pathogenesis of both AD and PD. This leads us to believe that Buntanetap has the potential to be a promising drug for the treatment of both AD and PD. Our approach is innovative in that we do not have a single therapeutic target for a single disease; instead, we are developing a technology platform that has the potential to target the mRNAs of multiple neurotoxic proteins, which are potentially impactful for multiple diseases.

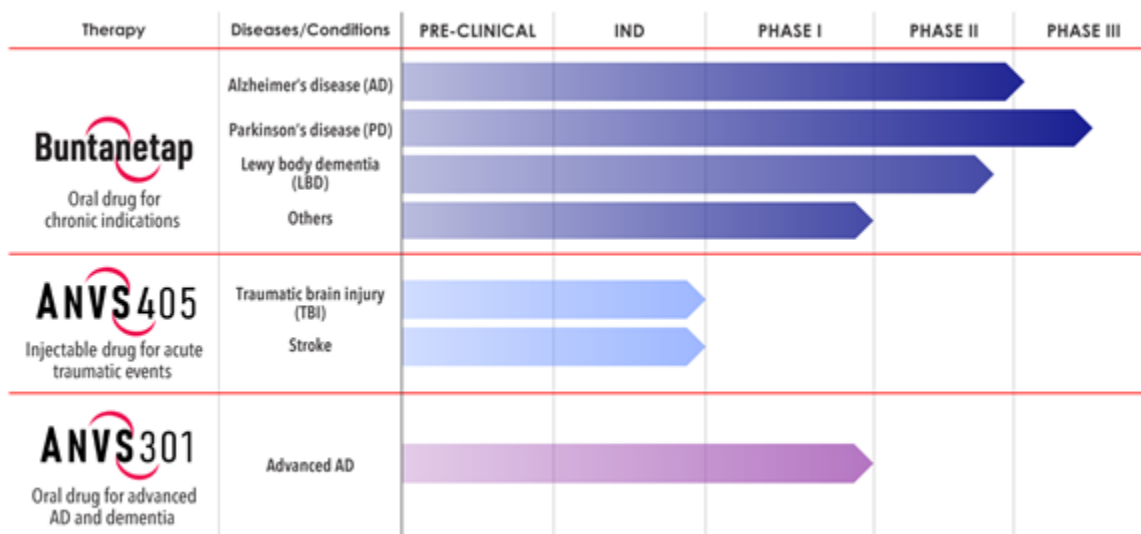


In our AD/PD Trials, we observed that Buntanetap reduced levels of neurotoxic proteins, improved axonal transport and synaptic function, reduced inflammation, improved the health of nerve cells and improved cognition and function in mild to moderate AD and PD patients.

We have observed that Buntanetap reduced the levels of multiple neurotoxic proteins in animals and reversed the toxic cascade. In addition, Buntanetap was observed to reverse the entire toxic cascade in animals and recover function, be it in the brain, the body, or the eyes.

## Pipeline

Our pipeline consists of: Buntanetap for chronic neurodegeneration - including AD and PD; ANVS405 for acute neurodegeneration; and ANVS301 for advanced AD.



### Buntanetap

Our lead product candidate, Buntanetap, is an orally administered drug being developed for chronic indications such as AD and PD, and it has been observed to improve axonal transport in these diseases in preclinical studies by inhibiting the overproduction of neurotoxic proteins that kill nerve cells. Buntanetap further demonstrated improvements of cognition, including memory and learning, in AD mice and movement, including colonic motility and grip strength, in PD mice. Buntanetap was tested in three Phase 1 clinical studies that showed it to be well tolerated. This safety data is applicable to the clinical development of Buntanetap for AD, PD, and potentially other chronic neurodegenerative diseases. We have completed three Phase 1/2 clinical trials for Buntanetap. We are presently treating PD patients in our Phase 3 PD Study and AD patients in our Phase 2/3 AD Study.

We believe that Buntanetap has the potential to be the only drug to improve both cognition in AD patients, and motor function in PD patients. Additionally, Buntanetap was observed to protect nerve cells from dying in the brain of traumatic brain injury mice and to protect nerve cells from dying in the eye of glaucoma rats.

### ANVS405

ANVS405 is an intravenous drug being developed for acute indications, and focused on protecting the brain after TBI and/or stroke. ANVS405 is the same compound as Buntanetap, given in cases of acute head and brain trauma. ANVS405 was given to rats intravenously after TBI to determine whether ANVS405 would reach the brain in less than 15 minutes, as opposed to 1.5 hours if given orally. TBI rats that were treated with ANVS405 after the insult exhibited enhanced memory and learning and lower microglia activation, a measure of inflammation. The program has been funded by a grant from the U.S. Army which has been completed, and we plan to seek additional grant funding to further the development of ANVS405 for acute indications of brain and nerve trauma. If and when we receive such sufficient funding, we plan to conduct a follow-on study to evaluate the effect of ANVS405 administered to TBI rats at various intervals post-injury to determine how long after a TBI we can effectively treat a patient. Our plan is to seek further funding to conduct the toxicology and pharmacokinetics ("PK") studies in animals, file the initial new drug application ("IND"), conduct the safety and PK studies in humans and continue with Phase 2 and Phase 3 efficacy studies.

## ***ANVS301***

ANVS301 is an orally administered drug being developed to increase cognitive capability in later stages of AD and dementia. ANVS301 was observed to improve memory and learning in very old rats by lowering the number of errors from six to three and shortening run times from approximately 75 to approximately 28 seconds. ANVS301 is in a Phase 1 clinical trial that was conducted and financed by the National Institutes of Health (“NIH”). The single ascending dose study has been completed, and we expect to evaluate the continued development of ANVS301 based upon funding availability. When both the single and multiple ascending dose safety studies are complete, we will review the data and decide whether to pursue the indication of advanced AD.

### **Clinical Trials of Buntanetap**

#### ***Development Plan for Alzheimer’s Disease***

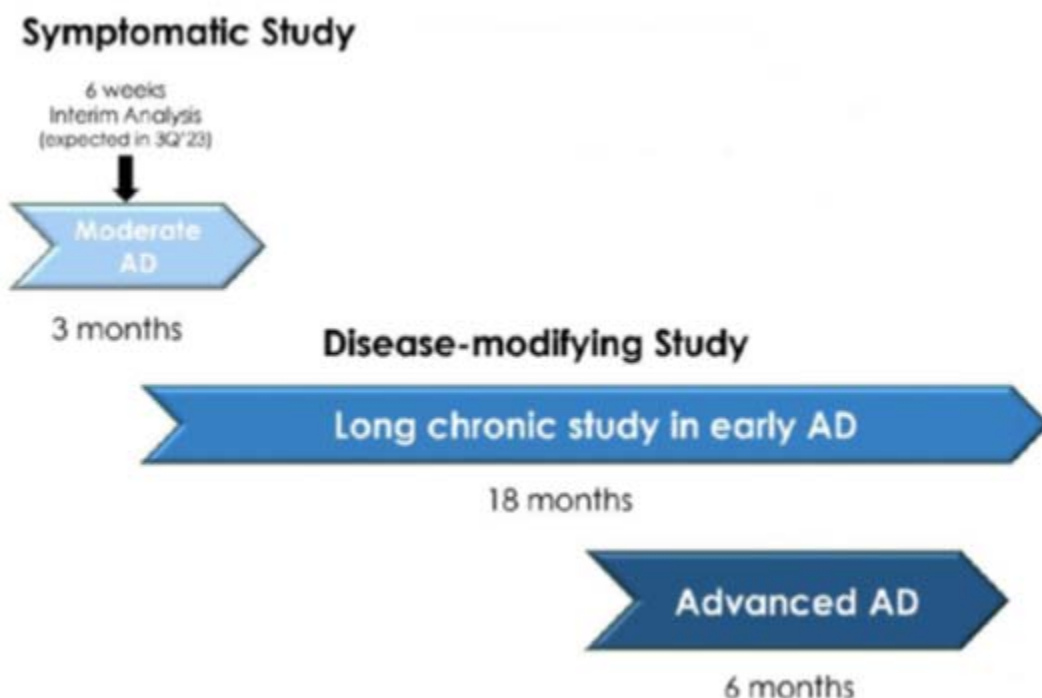
The development of Buntanetap for AD is expected to include a short study for moderate AD showing symptomatic efficacy, a long 18-month study in early AD showing disease-modifying efficacy, and a second short 6-month study in advanced AD. We expect to discuss the development plan with the FDA following receipt of the results from the interim analysis of the first study in Fall 2023.

In February 2023, we initiated the first of the three studies: a Phase 2/3 clinical trial of Buntanetap in 320 mild to moderate AD patients, which were separated into four cohorts of 80 patients (the “Phase 2/3 AD Trial”). The Phase 2/3 AD Trial is expected to be conducted at approximately 80 sites in the U.S. The Phase 2/3 AD Trial is a double-blind placebo-controlled efficacy study which treats mild to moderate AD. The inclusion criteria for mild to moderate AD is a MMSE score of 14 to 24. Patients participating in the trial are age 55-85, have a study partner, are of non-child-bearing age or agree to effective contraception, and have no evidence of suicidal ideation. Patients participating in the trial can remain on any drugs they regularly take, whether for AD or for other conditions, as long as they are stable on such medication. Patients with uncontrolled diabetes, cardiovascular issues or seizures, patients with clinically significant abnormal laboratory values, patients with cancer within the last year and patients suffering from alcohol or substance abuse are excluded from participating.

Patients will be randomly assigned to receive either 7.5, 15 or 30 mg of Buntanetap or placebo once per day. Patients will visit the clinic for the first-time dosing in clinic, followed by an at home dosing period of 12 weeks. The study plan incorporates an interim analysis at six-weeks, the results of which are expected in Fall 2023. The Phase 2/3 AD Trial is designed to assess the efficacy, safety, tolerability, and PK of Buntanetap. The co-primary endpoints of the Phase 2/3 AD Trial are evaluated using the following measures: Alzheimer's Disease Assessment Scale-Cognitive Subscale 11 (ADAScog 11), which measures cognitive functions and non-cognitive functions such as mood and behavior; and ADCS-Clinical Global Impression of Change (ADCS-CGIC), which focuses on clinicians' observations of change in the patient's cognitive, functional, and behavioral performance since the beginning of a trial. The FDA requested to include two co-primary endpoints to have an objective primary endpoint (ADAScog, cognition) and a subjective primary endpoint (ADCS-CGIC, activities of daily living). Together, these co-primary endpoints are intended to provide in a more complete picture of the study and treatment results. The secondary endpoints are evaluated using the following measures: the ADCS-Instrumental Activities of Daily Living Scale (ADCS-ADL), which measures 6 basic activities of daily living items, including basic self-care tasks such as feeding, mobility and bathing, and 17 instrumental activities of daily living items, which include a broad range of activities based on cultural norms and gender roles; MMSE; and the digital symbol substitution test (DSST), which asks individuals to record associations between different symbols and numbers within time limits to assess cognition.

The second trial we intend to conduct is an 18-month disease-modifying Phase 3 study in early AD patients, in which patients will be randomly assigned to receive either placebo or a dose of Buntanetap once per day, to be determined based upon the results of the Phase 2/3 AD Trial.

The third trial we intend to conduct is a six-month study in advanced AD patients, which is expected to take place during the second half of the 18-month disease modifying Phase 3 study. In this six-month study, patients will be randomly assigned to receive either placebo or a dose of Buntanetap once per day, to be determined based upon the results of the Phase 2/3 AD Trial.



### ***Development for Parkinson's Disease***

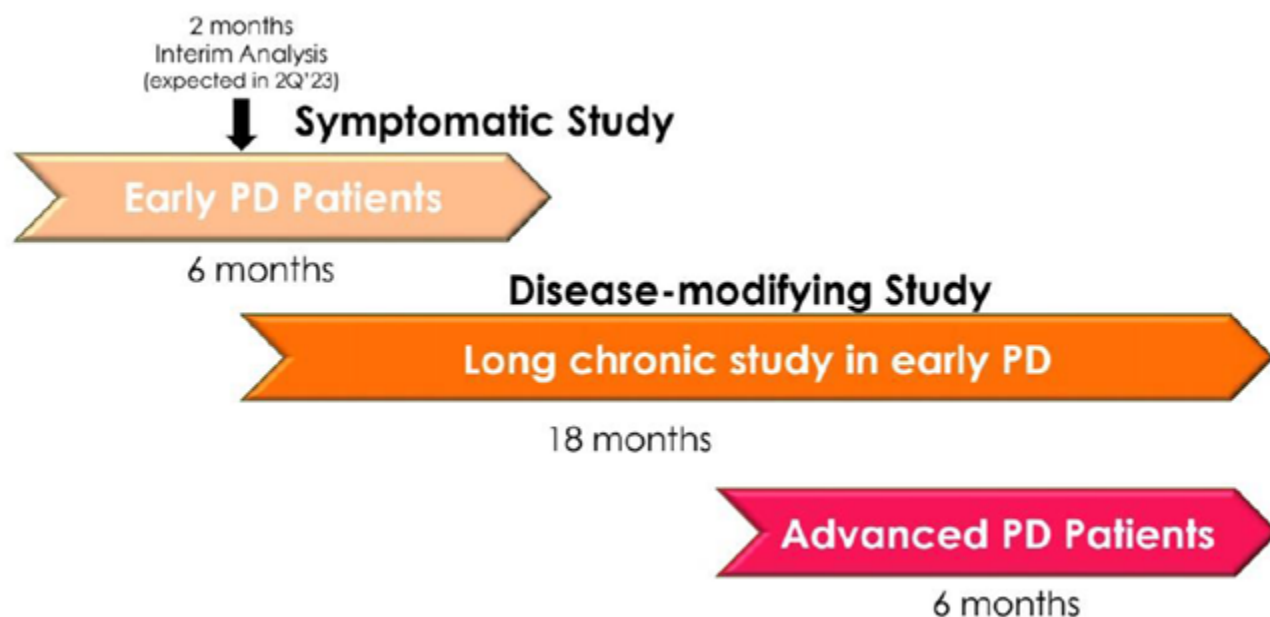
The development plan of Buntanetap for PD is expected to include a short study for early PD patients showing symptomatic efficacy, a long 18-month study in the same patient population showing disease-modifying efficacy, and a second short 6-month study in advanced PD.

In August 2022, we initiated a Phase 3 clinical trial of Buntanetap in 450 early PD patients, which were separated into three cohorts of 150 patients (the “Phase 3 PD Trial”). The Phase 3 PD Trial is expected to be conducted at approximately 53 sites in the U.S. and 49 sites in the EU. The Phase 3 PD Trial is a double-blind placebo-controlled efficacy study which treats early PD. The inclusion criteria for early PD are Hoehn & Yahr 1, 2 and 3 with less than 2 hours of OFF time, as well as a MMSE score of 22 to 30. Patients participating in the trial are age 40-85, are of non-child-bearing age or agree to effective contraception, and have no evidence of suicidal ideation. Patients participating in the trial can remain on any drugs they regularly take, whether for PD or for other conditions, as long as they are stable on such medication. Patients with uncontrolled diabetes, cardiovascular issues or seizures, patients with clinically significant abnormal laboratory values, patients with cancer within the last year and patients suffering from alcohol or substance abuse are excluded from the trial. Patients are randomly assigned to receive either 10 or 20 mg of Buntanetap or placebo once per day. Patients visit the clinic for the first-time dosing in clinic, followed by an at home dosing period of 6 months. The study plan incorporated an interim analysis at two months, the results of which were disclosed by the Company on March 31, 2023. The pre-planned interim analysis was conducted by our data analytics provider based on 132 patients from all cohorts collectively for which baseline and two-month data was available. As the interim analysis was conducted at two months of the six-month endpoint and only on 132 patients, it may not be indicative of the results at six months for the full patient population because as the trial progresses, clinical outcomes may materially change as patient enrollment continues and more patient data become available, or different conclusions or considerations may qualify such results once additional data have been received and fully evaluated. Based on the results of the interim analysis, we intend to proceed with the Phase 3 PD Study as planned in accordance with the previously established protocol. We remain blinded to the Phase 3 PD Study and we do not have safety or efficacy data from the trial. A separate safety interim analysis is in process and we expect that interim analysis to be released in the second quarter of 2023. The study is designed to assess the efficacy, safety, tolerability, and PK of Buntanetap. The Phase 3 PD Trial’s primary endpoints are evaluated using the following measures: the MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II and III, which is a 42-item rating scale designed to assess Parkinson's disease-related disability and impairment, and evaluates activities of daily living and motor function; and safety and tolerability, which is assessed using physical examinations, vital signs, clinical laboratory test results,

electrocardiogram findings, adverse events (AEs) leading to study discontinuation, drug related AEs, severity of AEs and AEs. Specifically, The FDA requested two co-primary endpoints to have an objective primary endpoint (MDS-UPDRS Part III, motor function) and a subjective primary endpoint (MDS-UPDRS Part II, activities of daily living). Together, these co-primary endpoints are intended to provide in a more complete picture of the study and treatment results. The secondary endpoints are evaluated using the following measures: the MDS-UPDRS total score, which includes the Part II and III measures as well as mentation, behavior, and mood symptoms, and complications of dopaminergic therapy; the participant global impression of change (PGIC), a participant-reported outcome which asks how their condition has changed compared to their condition at the beginning of treatment; and the Change on Clinical Global Impression of Severity (CGIS), which measures the severity of movement impairment as assessed by the site rater.

The second trial we intend to conduct is an 18-month disease-modifying Phase 3 study in early PD patients, in which patients will be randomly assigned to receive either placebo or a dose of Buntanetap once per day, to be determined based upon the results of the Phase 3 PD Trial.

The third study we intend to conduct is a six-month study in advanced PD patients, which is expected to take place during the second half of the 18-month disease modifying Phase 3 study. In this six-month study, patients will be randomly assigned to receive either placebo or a dose of Buntanetap once per day, to be determined based upon the results of the Phase 3 PD Trial.



### ***Phase 1/2 AD/PD Trials***

In 2021, we completed a Phase 1/2 clinical trial of Buntanetap in 14 early AD and 54 early PD patients (the “AD/PD Trials”) which were conducted at 12 sites in the U.S. The AD/PD Trials were double-blind placebo-controlled studies which treated mild to moderate AD and early PD patients for 25 +/- 2 days. The inclusion criteria for the AD portion of the AD/PD Trials were MMSE 18-28 and age 45 and older and for the PD portion of the AD/PD Trials were MMSE 18-30, age 45 and older and Hoehn & Yahr 1, 2 or 3. Patients participating in the trial were of non-child-bearing age or agreed to effective contraception, and had no evidence of suicidal ideation. Patients participating in the trial could remain on any drugs they regularly take, whether for PD, for AD or for other conditions, as long as they were stable on such medication. Patients with uncontrolled diabetes, cardiovascular issues or seizures, patients with clinically significant abnormal laboratory values, patients who had cancer within the prior year and patients who suffered from alcohol or substance abuse were excluded from the trial.

The AD/PD Trials were designed to assess the safety, tolerability, and PK of Buntanetap. The studies met their primary endpoints of safety and tolerability, as measured by the percentage of patients with treatment-emergent adverse events in the



Buntanetap treatment arms as compared to the placebo groups, and secondary endpoint of pharmacokinetics of Buntanetap, as measured by the concentration of Buntanetap in plasma. The studies also met exploratory endpoints of measures of biomarkers related to neurotoxic protein cascade, and improvements in cognition in AD patients and function in PD patients. We believe the AD/PD Trials were the first double-blind, placebo-controlled studies that showed improvements in AD patients as measured by ADAS-Cog, and in PD patients as measured in UPDRS.

The studies were conducted in two parts. The first part of the AD/PD Trials was in 14 early AD patients and 14 early PD patients. Patients were randomly assigned to receive either 80 mg of Buntanetap or placebo once per day. The second part of the AD/PD Trials was a dose response analysis in 40 early PD patients in which patients were randomly assigned to receive 5 mg, 10 mg, 20 mg, or 40 mg of Buntanetap once per day. In both parts of the AD/PD Trials, patients visited the clinic for the first-time dosing in clinic, followed by an at home dosing period of 25 +/- 2 days. We measured levels of neurotoxic proteins, neurotransmitters, neurotrophic factors, inflammation, and nerve cell death in all patients, as well as cognitive and functional improvements.

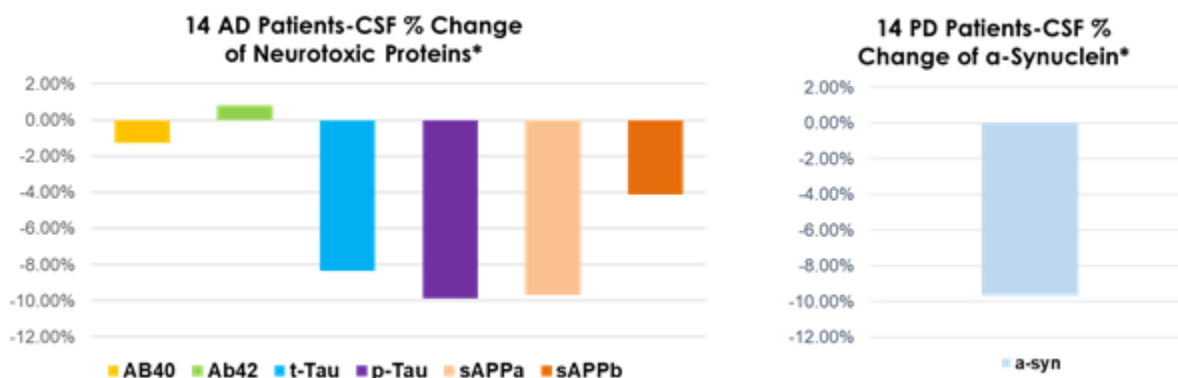
### Safety and PK

Safety results show that Buntanetap was well-tolerated in all dose groups. No serious adverse events were reported. The adverse events seen included problems related to CNS sampling: headaches, back and leg pain. PK parameters for Buntanetap in plasma of AD and PD patients were similar to those seen in Phase 1 in our single ascending dose (“SAD”) and multiple ascending dose (“MAD”) studies in healthy volunteers, and in a proof-of-concept study in mild-cognitive impaired (“MCI”) patients.

### Reduction of Neurotoxic Proteins

We observed that Buntanetap administration for 25 days lowered secreted APP  $\alpha$  and  $\beta$  as well as total-tau and phosphorylated-tau levels in AD patients, and alpha-synuclein levels in PD patients. APP and its downstream products and tau are the neurotoxic proteins involved in AD, while  $\alpha$ SYN is the primary neurotoxic culprit of PD.

#### **Changes in Biomarkers After 25 Days Treatment with Buntanetap**



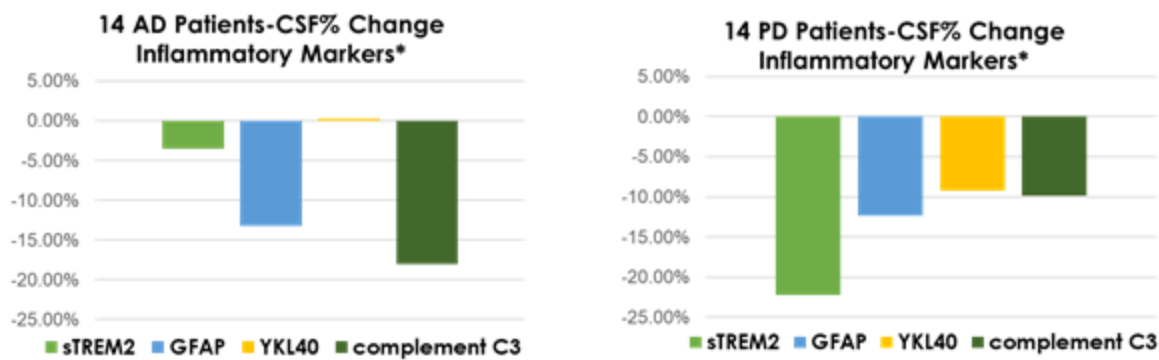
*\* All values are in comparison to placebo based on all data points.*

Cerebrospinal fluid (“CSF”) was extracted before starting the study at baseline and at time 0 to 6 hours at the end of the study in both placebo and Buntanetap treated patients. The values from time 0 to 6 hours were pooled to lower variability and the placebo values were deducted from the treated values. In all but one case, Ab42, we saw that the levels in Buntanetap treated patients were lower than in placebo patients. With respect to Ab42, we observed that levels were slightly higher, which is consistent with our hypothesis that Ab42 levels are lower in advanced AD and higher in early AD. We believe that higher Ab42 levels we observed suggest that the course of AD was reversed and the patients improved.

Inflammation

We observed that Buntanetap reduced inflammation in both AD and PD patients, shown by Complement C3, YKL-40, GFAP and sTREM2.

*Changes in Inflammatory Markers after 25 Days Treatment with Buntanetap*



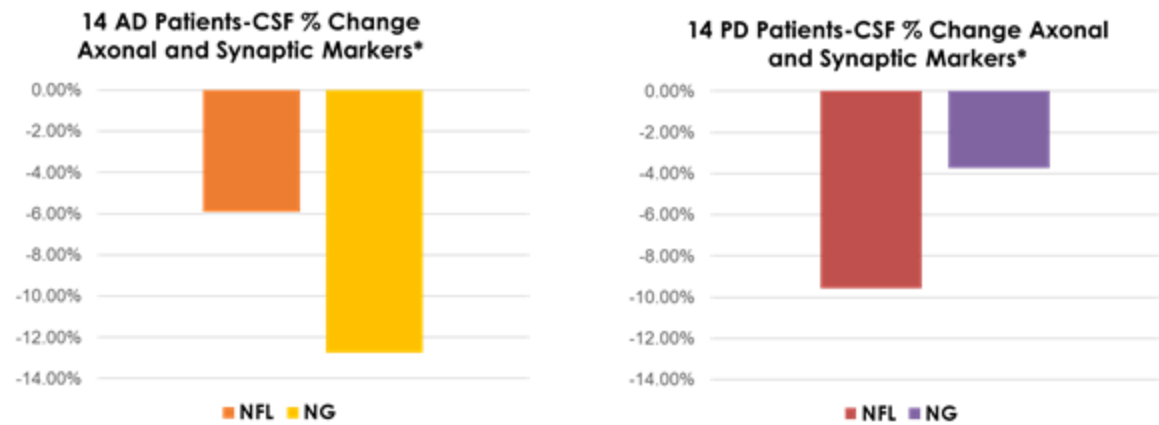
*\*All values are in comparison to placebo based on all data points.*

Again, CSF was extracted at baseline and for 6 hours after the study and the values of the placebo patients were subtracted from the Buntanetap treated patients. We observed that inflammatory markers were generally reduced in both patient populations.

Axonal and Synaptic Function

We observed that Buntanetap reduced neurofilament light (“NFL”) levels in both AD and PD patients, suggesting a potential improvement in axonal integrity. We also observed that Buntanetap reduced neurogranin (“NG”) levels in both AD and PD, potentially suggesting more intact synaptic functions.

*Changes in Synaptic Markers after 25 Days Treatment with Buntanetap*



*\*All values are in comparison to placebo based on all data points.*

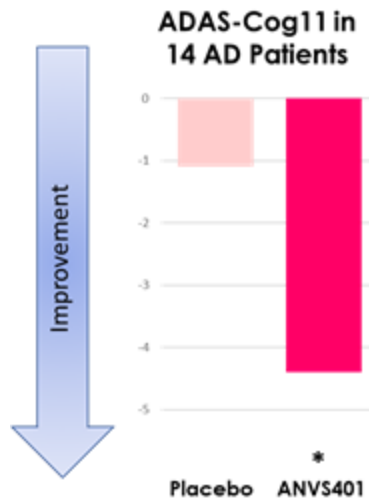
The same CSF as above was used to measure neurofilament light and neurogranin before and after treatment and to compare Buntanetap patients to placebo. In both patient populations neurofilament light and neurogranin are lower in treated than in placebo patients.



We believe these results suggest that Buntanetap has the potential to reduce neurotoxic proteins, rescue axonal transport, reduce inflammation, and protect synaptic functions.

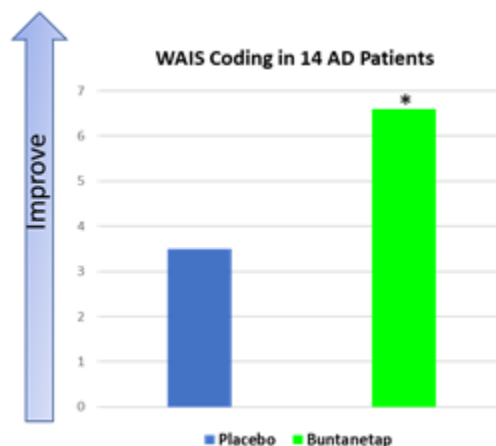
### Cognition in AD Patients

We performed ADAS-Cogs and WAIS coding tests to evaluate Buntanetap’s effects on AD patients’ cognition.



\* P<0.05

ADAS-Cog11 was performed at the beginning of the study at baseline and at the end at 25 days in the Buntanetap-treated and the placebo groups. Although the study was not powered for efficacy, ADAS-Cog11 improved by 4.4 points, a statistically significant improvement of 28.57%. A result is considered to be statistically significant when the probability of the result occurring by random chance, rather than from the efficacy of the treatment, is sufficiently low. The conventional method for determining the statistical significance of a result is known as the “p-value,” which represents the probability that random chance caused the result (e.g., a p=0.01 means that there is a 1% probability that the difference between the control group and the treatment group is purely due to random chance). Generally, a p-value less than 0.05 is considered statistically significant. An improvement in ADAS-Cog11, which is reflected by a lower ADAS-Cog11 result, indicates increased cognitive performance. At 25 days, the treated group’s improvement from baseline was 3.3 points, or 20.71%, better than the placebo group’s improvement from baseline.

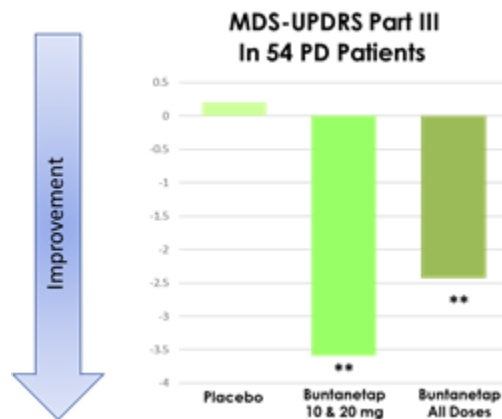


\* P<0.05

The WAIS coding test measures speed in movement and thinking. Treated AD patients showed a 6.6 point, or 16.17%, statistically significant improvement from baseline. Furthermore, the treated group's improvement from baseline was 3.1 points, or 8.8%, better than the placebo group's improvement from baseline.

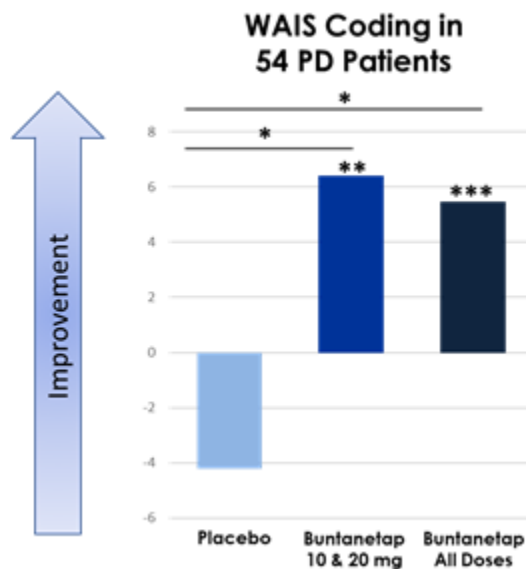
### Motor Function in PD Patients

In Parkinson's disease, we pooled the original 14 PD patients with the additional 40 PD patients, and looked at the MDS-UPDRS and WAIS coding tests to evaluate Buntanetap's effects on PD patients' mobility and functionality. We the 54 PD patients received doses of either 5mg, 10mg, 20mg, 40mg or 80mg Buntanetap treatment or placebo once per day. We observed a statistically significant improvement in Part II, III and IV individually. Specifically, Part III of the MDS-UPDRS measures the motor functions and has long been used as a standard to assess drugs' effects on patients' mobility.



\*\*p<0.01

We combined the two best doses, 10 and 20 mgs, and all doses, and saw an improvement of 3.6 (16.4%) for 10 and 20 mg, and of 2.4 (13.3%) for all doses combined compared to baseline.



\* p<0.05 \*\* P<0.01 \*\*\* P<0.001

In the WAIS coding test, PD patients show a statistically significant improvement both from baseline (17.1% for 10+20mg; 13.3% for all doses combined) and from placebo (27.1% for 10+20mg; 23.3% for all doses combined).

### ***Phase 1/2 ADCS Trial***

We also completed a double-blind, placebo-controlled Phase 1/2 study in early AD patients in conjunction with the ADCS. We treated patients for four weeks with Buntanetap and measured target and pathway engagement in the spinal fluid. This means that we measured levels of neurotoxic proteins, neurotransmitters, neurotrophic factors, inflammation and nerve cell death as well as cognitive improvement. Since Buntanetap is designed as a translation inhibitor, we also measured the rate of synthesis and degradation of A $\beta$  (SILK – stable isotope labeling kinetic study) to determine if our drug changes the speed of translation. Under an agreement with the University of California San Diego, where ADCS is located, we contracted to provide study supplies and PK analysis at our cost but the remaining costs of the ADCS Trial are paid for by the NIH. The study ended after 16 patients were enrolled and treated. Patients participating in the study were of non-child-bearing age or agreed to effective contraception and had no evidence of suicidal ideation. Patients participating in the study could remain on any drugs they regularly take, either for AD or for other conditions, as long as they were stable on such medication. Patients with uncontrolled diabetes, cardiovascular issues or seizures, patients with clinically significant abnormal laboratory values, patients who had cancer within the prior year and patients who suffered from alcohol or substance abuse were excluded from the study. The study was conducted at six sites in the U.S., including the University of California San Diego, Johns Hopkins, Indiana University, Washington University, Cleveland Clinic, and Columbia University. While only 16 patients were treated in total, based on the SILK data, we observed that Buntanetap has the potential to slow the translation of APP/A $\beta$ , leading to overall lower levels and lower overall synthesis of the neurotoxic protein. The Alzheimer's Disease Assessment Scale –Cognitive Subscale (ADAScog) of the treated patients demonstrated what we observed in our small AD/PD study – statistical improvement in cognition at one month of treatment.

### ***Phase 1 Studies***

Three phase 1 clinical studies have been completed with Buntanetap. Clinical studies with single and repeated daily oral administration of Buntanetap, showed Buntanetap to be well tolerated up to doses of 80 mg once a day or 60 mg four times a day. A single dose of 160 mg was associated with an increased incidence of nausea and vomiting; therefore, higher doses were not tested. Buntanetap is not an AChE inhibitor, but its N1 dimethyl metabolite has some AChE inhibitor activity and may be responsible for these observations. The only consistent AEs seen were dizziness/fainting and headaches. These effects were seen to varying degrees at all doses of Buntanetap and in the placebo group. There were no serious AEs in any of the clinical studies. In the repeat dose studies, treatment with 60 mg four times a day was not associated with any side effects not also seen in placebo. The adverse events seen included nausea, vomiting and dizziness.

### ***Proof-of-Concept Study in Humans***

In the human proof-of-concept (“POC”) study, four patients with MCI were treated for 10 days with Buntanetap with a dose of 60 mg four times a day (240 mg/day), which we observed in a previous safety study to be a well-tolerated level. CSF and plasma were drawn over 12 hours on Day 0 before any administration of Buntanetap and on Day 11 after the last administration of Buntanetap. During each 12-hour period, a total of nine CSF samples were taken and levels of Buntanetap and metabolites were measured in plasma and CSF at all time points. The human POC study was discontinued prior to completion as a cost saving measure.

### **Pharmacokinetics**

Buntanetap's PK in plasma corresponded to what we had seen in the previous clinical safety studies: a half-life of five hours. In CSF, however, Buntanetap showed a much longer half-life of over 12 hours. We conducted an identical experiment in rats, where it is possible to measure the PK of Buntanetap in plasma, CSF and brain. By taking the human plasma/CSF and rat plasma/CSF/brain levels, we were able to extrapolate to the human brain levels and calculate them to be eight times higher than plasma levels. This is generally consistent with the data we have in mice, where in several studies, Buntanetap levels were found to be approximately six to eight times higher in brain than in plasma.

Buntanetap's extended presence in the brain is matched by an extended effect, reducing levels of APP, tau and  $\alpha$ SYN for the whole 12-hour period tested. The extended effect of Buntanetap in the four human patients was generally consistent with the preclinical data in rodent brains.

We believe the persistence of Buntanetap in the CSF and brain and the extended pharmacodynamic effect observed has the potential to make Buntanetap a good candidate for once-a-day dosing. Extrapolated brain levels of Buntanetap at 60 mg four times a day were far in excess of levels we believe are required to down-regulate APP and  $\alpha$ SYN. The doses of Buntanetap needed to lower the levels of neurotoxic proteins are similar for the toxic proteins, suggesting similar dosing in AD and PD. We further compared Buntanetap brain levels of mice that showed improved memory, learning and colonic motility and estimated that the optimum brain levels measured were between 150 and 500 nM. Using three different extrapolation/comparison calculations we estimated that a daily dose of 5 mg to 25 mg may be able to achieve potentially desired brain levels in humans.

### Pharmacodynamics

Buntanetap pharmacodynamics was performed on the same 18 CSF samples taken from each person as above. Since we had data for four patients with 18 time points each, it was possible to conduct statistical analysis of the data using a repeated measure mixed model analysis of variance. The p-value represents the probability that the difference between compared groups is due to chance rather than drug effect, and when that probability is less than 5%, or  $p < 0.05$ , the result is considered statistically significant. FDA evidentiary standards for drug approval require that the trial design must permit a valid comparison with a control group to permit a quantitative assessment of the effect of the drug, which may include demonstration of statistical significance.

### Comparison with Healthy Volunteers

We also compared the levels found in four healthy volunteers with the levels seen in the four MCI patients before and after 10 days of Buntanetap administration. The healthy volunteers did not go through the entire study as did the MCI patients. They gave one CSF sample taken by lumbar puncture in the morning and that sample was only used to measure sAPP $\alpha$ , sAPP $\beta$  and tau.

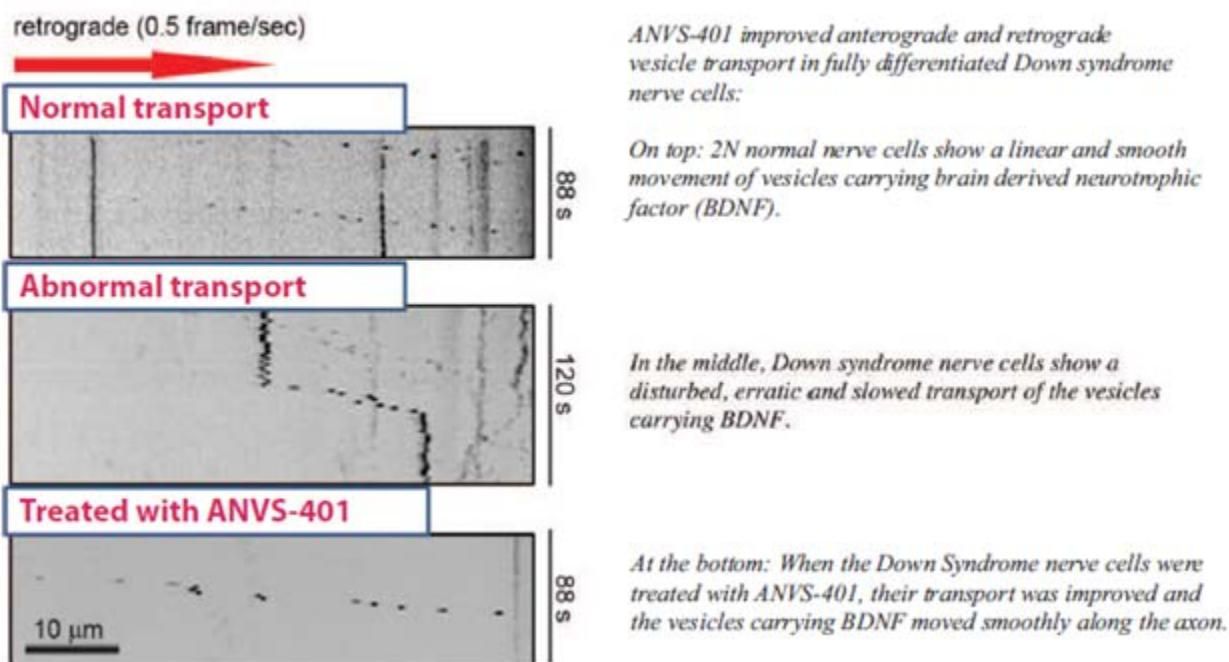
We used a single measurement from the same time point in each of the mornings of Day 0 and Day 11 for each MCI patient because this was similar to the timing for the healthy volunteers. In this very limited comparison, we were able to show that all four patients experienced a decrease in sAPP $\alpha$ , sAPP $\beta$  and tau. These reductions brought the average levels of sAPP $\alpha$ , sAPP $\beta$  and tau in the treated MCI patients close to the average levels we measured in healthy volunteers.

We used the same 18 samples collected from the CSF of the mildly cognitive impaired patients and measured four inflammatory factors and one control factor. In accordance with our hypothesis the levels of inflammatory markers were significantly reduced. We also measured Factor FH, a complement regulatory protein, as our control factor. As we had expected, Factor FH was not downregulated by Buntanetap.

### ***Axonal Transport in Human Nerve Cells***

When the information highway of a nerve cell slows down, the nerve cell is unable to properly communicate with other nerve cells, internal organs and the periphery and it gets sick and dies.

The transfer of information in a nerve cell is called axonal transport and when transport and synaptic transmission are impaired, the cell releases lower levels of neurotransmitters, leading to impaired nerve cell health. The diseased cell is then attacked by the immune system, which is activated when it detects a diseased cell, and it eventually kills the cell. Impairment in axonal transport, therefore, leads to inflammation and eventually to nerve cell death.



## Preclinical Animal Studies

By inhibiting the overexpression of neurotoxic proteins, Buntanetap improved or prevented the symptoms associated with chronic as well as acute neurodegeneration in several animal models.

### *APP/PS1 Transgenic Mouse Model of AD*

APP/PS1 AD transgenic (“tg”) mice were treated for one month with Buntanetap, before behavioral evaluation. Buntanetap was observed improving spatial-working memory in a 2-day radial arm water maze test in this mouse AD model at a 25 mg/kg oral dose and showing a dose response at 10 mg/kg oral dose. In the same study, Buntanetap was observed improving synaptic function and long-term potentiation in hippocampal slices at both doses in a dose-dependent fashion. Buntanetap treatment did not affect wild-type mice.

### *Trisomic Mouse Model of AD-DS*

DS trisomic mice display several abnormal behaviors reminiscent of AD, including memory loss. They have elevated levels of APP that has been shown in mice to contribute to deficient memory and learning, cognitive impairment as well as dementia. DS trisomic mice are used as a model for AD, because they exhibit similar deficits as seen in AD. Thus, we considered whether Buntanetap could re-establish healthy behavior in these mice like that seen in wild-type mice. We measured the rate of spontaneous alternations in a Y-maze and found that the alternation rate is significantly lower in DS trisomic mice versus wild-type mice reflecting impaired working memory. While Buntanetap treatment increased alternation rate in DS trisomic mice it had no obvious effects in wild-type mice. We also found an effect on the exploratory activity reflected by the number of arm entries, again reflecting impaired working memory. All DS trisomic mice treated with Buntanetap displayed improved working memory to a variable extent.

### *SNCA453T and SNCA430P Mouse Models of PD*

We used these PD tg mice as models of early gastrointestinal dysfunction, which is common in PD patients and precedes the onset of motor symptoms by many years to decades. Untreated PD tg mice resemble pre-Parkinson’s patients, showing symptoms of constipation by three months of age. Here we assessed the colonic motility by measuring the time required to expel a glass bead inserted into the colon at four and seven months of age. Buntanetap statistically significantly ( $p=0.034$  at four months and  $p=0.0001$  at

seven months) decreased the bead expulsion time between Buntanetap treated and placebo treated mice; thus, it improved the colonic motility of PD tg mice. Furthermore, even after we stopped treatment for nine weeks, the constipation was still reduced.

### ***TBI in Rats***

TBI causes severe cognitive and neurological impairment, which can incapacitate the patient, reduce quality of life, and increase the risk of morbidity and mortality. TBI is known to increase the risk for neurodegenerative disorders such as AD and PD. Several studies have analyzed changes in the brain after TBI and identified up-regulation of neurotoxic proteins, such as APP, tau, and  $\alpha$ SYN.

In our study (manuscript in preparation), rats were subjected to either fluid percussion injury (“FPI”) or sham operation to one side of the brain. Three different ANVS405 doses or saline were given intraperitoneally to rats subjected to FPI for four weeks, with the first dose administered one hour post-injury. At the termination of the treatment, all the rats were first tested for their performance in the water maze, and then they were sacrificed for brain staining of living cells and determination of microglia activation. 10 mg/kg ANVS405 improved memory and learning as measured by water maze performance. Furthermore, sections of the brain were stained with tyrosine hydroxylase (“TH”), wherein TH stains only live cells. The amounts of TH immunoreactivity in the whole striatum of the brain slices were measured. The rats treated with all three doses of ANVS405 showed higher TH staining in the ipsilateral area of the brain than the vehicle treated animals. Thus, ANVS405 protects the striatum following FPI in rats.

Because FPI can induce microglial activation, we next checked whether ANVS405 would reverse this pathology. In our study, we found that ANVS405 increased the number of resting microglia and reduced the number of activated microglia.

### ***Stroke Mice***

Buntanetap was tested in a stroke model, in which mice were challenged with MCAo-induced stroke (middle carotid artery occlusion induced stroke) and after four weeks, the number of surviving neurons was quantified. After four weeks the locomotor function, behavior, and cognition of these mice were also evaluated.

Buntanetap in combination with pifithrin- $\alpha$  (PFT- $\alpha$ ) given to mice after the induced stroke improved mice locomotor activity and cognitive function. While both treatments yielded improvements in locomotor and cognitive function, the combined Buntanetap/PFT- $\alpha$  treatment proved able to enhance stroke-induced endogenous neurogenesis and improve the functional recovery in stroke animals. The combined treatment also significantly improved cognitive function more than the single treatment with PFT- $\alpha$ .

### **Markets**

With there being a very large potential market for neurodegenerative diseases, most pharma companies have a program studying some aspect of nerve and brain degeneration. Some newer approaches target tau, whose expression is more closely associated with cognitive decline. Similarly, for PD, several companies are trying to inhibit  $\alpha$ SYN. So far, we believe that neither drugs attacking tau nor  $\alpha$ SYN have shown positive results. Hence there is a substantial need for a different disease-modifying strategy. There is more than one neurotoxic protein in the brain of AD and of PD patients, and the same neurotoxic proteins are involved in the pathogenesis of AD and PD. A significant portion of AD patients’ brains display mixed PD pathology and vice versa. Therefore, just attacking one of these proteins may result in no or lower efficacy than attacking them all. To prove that this approach is possible, we are studying the effects of Buntanetap on the levels of several neurotoxic proteins and other surrogate markers, in parallel, in AD and PD patients.

### ***Alzheimer’s Disease Market***

AD is a neurodegenerative disorder with cognitive, functional, and behavioral alterations. AD is age related, and its incidence is increasing with the aging of the population. It is estimated that currently 44 million victims of AD dementia exist in the world and by 2050, more than 100 million people worldwide will be living with AD. In the United States, it is estimated that there are six million patients with AD. Nearly eightfold as many people have preclinical AD as have symptomatic AD and are at risk for progressing to manifest disease. Disease modifying treatments (“DMTs”) that will prevent or delay the onset or slow the progression of AD are urgently needed. Similarly, medications to effectively improve cognition or ameliorate neuropsychiatric symptoms of patients in the symptomatic phases of AD are needed to improve memory and behavior.

The incidence rate of AD increases significantly with age. Individuals between ages 64 to 75 have an incidence rate of 0.4%, which increases to 3.2% for people between ages 75 and 84 and finally to 7.6% for people aged 85 and above. These incidence rates are cumulative as an individual ages, which means that an individual reaching 90 years of age will have a 38% chance of suffering from AD while an individual reaching the age of 95 will have a 76% chance of suffering from AD. AD is becoming increasingly common as the global population ages and as the health systems in developing countries improve. There is a significant need to identify drugs that prevent, delay the onset, slow the progression, or improve the symptoms of AD.

### ***Parkinson's Disease Market***

PD is also a progressive neurodegenerative disorder with movement and non-movement symptoms, functional, behavioral and cognitive alterations. PD, like AD, is age related and is becoming markedly more common with the aging of the world's population. PD affects about 1% of the population over the age of 60, while in individuals over the age of 85, this prevalence reaches 5%, highlighting the impact that advancing age has on the risk of developing this condition.

PD affects about 10 million people worldwide, of which nearly one million are in the U.S. While a 2014 study estimated that the incidence in the U.S. will rise to 1.2 million by 2030, a later 2022 study found that there are nearly 90,000 new cases of PD diagnosed each year in the U.S., potentially supporting an even greater future incidence rate.

The National Parkinson's Foundation estimates that the economic burden of PD is at least \$25 billion a year in the United States.

To date, there are no available treatments capable of curing PD, with current therapies seeking only to ameliorate dopamine-related motor symptoms of the disease. There is a clear and unmet medical need for new DMTs that can slow or prevent PD progression.

### ***Mixed Pathologies Market***

In addition to the unmet need of AD and PD patients, approximately 50% of patients exhibit mixed pathologies, with some pathologies resembling AD and some resembling PD.

Dementia is increasingly being recognized in cases of PD; such cases are termed PD dementia ("PDD"). The spread of fibrillar  $\alpha$ SYN pathology from the brainstem to limbic and neocortical structures seems to be the strongest neuropathological correlate of emerging dementia in PD. Up to 50% of patients with PDD develop sufficient numbers of A $\beta$  plaques and tau-containing neurofibrillary tangles for a secondary diagnosis of Alzheimer's disease, and these pathologies may act synergistically with  $\alpha$ SYN pathology to confer a worse prognosis.

Another study looking at the incidence of mixed pathologies diagnosed community-dwelling older persons. Those with dementia most often have multiple brain pathologies, which greatly increases the odds of dementia. Specifically, in people with dementia, over 50% had multiple diagnoses (AD, PD/Lewy body dementia, PDD or infarcts). After accounting for age, persons with multiple diagnoses were almost three times more likely to exhibit dementia compared to those with one pathologic diagnosis.

We believe that a therapy that only addresses A $\beta$ , tau or  $\alpha$ SYN is less likely to help people with mixed pathologies. Since Buntanetap is designed to inhibit more than one neurotoxic protein, we believe that it may have the potential to slow or eventually stop AD, PD and mixed pathology diseases.

## **Approaches and Competition**

### ***Alzheimer's Disease Approaches***

Drug development for AD has proven to be very difficult. Drugs which have been approved for the treatment of AD include cholinesterase inhibitors (tacrine, donepezil, rivastigmine, galantamine) and an N-methyl-D-aspartate receptor antagonist (memantine). Many failures in AD drug development have occurred, with both small molecules and immunotherapies failing to show a drug/placebo difference or having unacceptable toxicity.

Most clinical trials conducted have addressed amyloid targets. Since A $\beta$  accumulates for years before the symptoms of AD are visible, some pharmaceutical companies are testing their drugs earlier, including cognitively normal people or those who have genetic profiles that place them at high risk for developing AD.

An increasing number of agents are directed at tau-related targets. Neurofibrillary tangles are one of two major pathological hallmarks of AD. Correlation studies conducted by Braak and Braak demonstrate that neurofibrillary tangle burden more closely correlates with cognitive decline than amyloid plaque load. Several phase 3 studies conducted with tau approaches have failed. There are still several anti-tau approaches in the clinic.

In summary, at present we believe there are no disease-modifying agents on the market. The first large effort to develop a DMD for AD has targeted A $\beta$ 42, but all A $\beta$ 42 approaches to date have failed. The first companies testing tau have shown negative results. Many companies have pulled out of AD research and are waiting to see what approach might have a better outcome. Since the AD brain contains several neurotoxic proteins—amyloid precursor protein and its toxic fragments A $\beta$ 42 and IC99, as well as tau and  $\alpha$ SYN. We believe that a DMD drug needs to target more than just one toxic protein to be efficacious and we are developing Buntanetap with this approach in mind.

A concerning observation derived from a review of the AD pipeline is the lack of agents targeting the moderate to advanced stages of AD. With over 15 million people affected by AD dementia worldwide, there is an urgent need to develop more effective symptomatic treatments for moderate to advanced stage disease. The paucity of agents directed at this population represents a significant weakness of the AD drug development pipeline.

### ***Parkinson's Disease Approaches***

Levodopa ("L-DOPA") was introduced for use in treating PD more than 40 years ago and remains the mainstay of therapy for improving the symptoms of the disease. Unlike dopamine, which cannot cross the blood—brain barrier, L-DOPA is effectively absorbed into the brain, where it metabolizes into dopamine. It is typically administered five times a day and works well in controlling symptoms for one to five years. Unfortunately, the effects of L-DOPA in any patient diminish with time. There are several other drugs available to treat PD, which also seek to modulate dopamine levels. Combination drug therapy is common in PD. For instance, the use of other drug classes such as the catechol-O-methyltransferase (COMT) inhibitors and the monoamine oxidase (MAO) inhibitors allow patients to reduce L-DOPA dosing levels.

The market for PD drugs is estimated at \$2 to \$3 billion worldwide, despite high-volume generics. The most important current therapy for PD, L-DOPA, is prescribed as a generic. While volume growth in the category is expected to remain healthy, dollar growth will likely remain relatively flat as some of the category's larger brands contend with generic inroads. The size of the current market reflects the absence of innovative branded therapies more than it does the medical need.

So far, we believe that only Buntanetap and Exenatide are in the later stages of clinical development for disease-modification and no products have yet shown efficacy in PD patients long term. Although several drugs have shown potential neuroprotective ability in preclinical studies, demonstrating these effects in clinical studies remains a challenge. Beyond drug therapies, a few cell and gene therapy approaches are also being explored. Progress across these newer technology platforms has been slow.

### **Intellectual Property**

We strive to protect and enhance the proprietary technologies, inventions and improvements that we believe are important to our business, including seeking, maintaining and defending patent rights, whether developed internally or licensed from third parties. Our policy is to seek to protect our proprietary position by, among other methods, pursuing and obtaining patent protection in the United States and in jurisdictions outside of the United States related to our proprietary technology, inventions, improvements, platforms and our product candidates that are important to the development and implementation of our business.

Annovis has filed seven families of patents and patent applications to prolong the patent life of Buntanetap. The pending patent applications were invented and filed by Annovis and include claims directed to:

- a method of treating neurodegenerative diseases such as AD and PD;



- a method of treating and/or preventing acute brain and nerve injuries;
- a method of prevention and treatment of disease states due to metal dis-homeostasis such as AD or PD as well as other acute or chronic neurodegenerative diseases;
- a method of treating viral and bacterial infections of the brain, including COVID-19;
- a method of inhibiting cancer metastasis;
- a combination with some drugs; and
- a method of treating neuropsychiatric indications.

As of February 14, 2023, our patent portfolio comprised 44 total issued patents plus 13 pending patent applications in various jurisdictions.

The issued patents have expiration dates, assuming all required fees and other charges are paid, between 2031 and 2038. Assuming each of our current patent applications are approved, our patent coverage will extend until 2043. The first patent application family we filed, which would be expected to expire, assuming all required fees and other charges are paid, in 2031, covers the use of Buntanetap at much lower doses and expands its use to the treatment of AD, PD and other neurodegenerative disorders such as Huntington's disease, prion diseases, amyotrophic lateral sclerosis, tauopathies and frontotemporal dementia, based on our preclinical research. In August 2019, the U.S. Patent and Trademark Office ("USPTO") granted the first of our Annovis patents from this family covering PD and Lewy body diseases. Subsequently the USPTO also granted patents covering tau and tauopathies, chronic traumatic encephalopathy, prion diseases, amyotrophic lateral sclerosis, Alzheimer's and Huntington's disease. The second patent application family covers ANVS405's use in acute brain and nerve trauma and would be expected to expire, assuming all required fees and other charges are paid, in 2036, before any patent term adjustments or extensions. In December 2020, the European Patent Office ("EPO") approved the whole patent, and it has since been approved in number of other countries. However, the USPTO entered a species restriction as to the condition being treated and we are therefore currently pursuing claims directed to traumatic brain injury. We intend to file additional divisional applications when we have successfully reached a conclusion to the pending application, assuming we are not able to cover the remaining acute conditions (stroke, nerve injury and spinal cord injury) for which patent coverage is being sought in the pending application. The third patent application family relates to the use of the mechanism of action of Buntanetap and ANVS405 to prevent and treat neurodegenerative diseases and would be expected to expire, assuming all required fees and other charges are paid, in 2038, before any patent term adjustments or extensions. The first divisional of this application was approved in December 2022; it covers the prevention of neurodegenerative diseases and we are awaiting the official publishing of the patent. In May 2020, we filed a patent application with the USPTO concerning a method of inhibiting, preventing, or treating neurological injuries due to viral, bacterial, fungal, protozoan, or parasitic infections in humans and in animals via administration of Buntanetap or related compounds which would be expected to expire, assuming all required fees and other charges are paid, in 2041, before any patent term adjustments or extensions; we have not received any office actions, yet. Recently we also filed three provisional patents - Buntanetap in cancer, Buntanetap and combinations, Buntanetap in neuropsychiatric indications.

Furthermore, we rely upon trade secrets and know-how and continuing technological innovation to develop and maintain our competitive position. We seek to protect our proprietary information, in part, using confidentiality agreements with our collaborators, employees and consultants and invention assignment agreements with our employees. We also have confidentiality agreements or invention assignment agreements with our collaborators and selected consultants.

## **Sales and Marketing**

If Buntanetap is approved for AD or PD, we plan to enter into sales and marketing agreements with one or several pharmaceutical companies to sell to neurologists, geriatric specialists and to primary care physicians. We also may explore the use of a variety of types of collaboration, co-promotion, distribution and other marketing arrangements with one or more third parties to commercialize our product candidates.

## **Manufacturing**

Buntanetap is a small molecule that is manufactured using a patented process. We do not own, operate, and currently have no plans to establish, any manufacturing facilities. We therefore rely, and expect to continue to rely, solely on third-party contractors for manufacturing clinical supplies for our current and future potential product candidates, and plan to do so for commercial supplies also if any of our product candidates received marketing approval. We also rely on these third parties for encapsulating, packaging and stabilizing clinical trial materials. Presently we are working with a U.S. supplier for the manufacture of good manufacturing practice (“cGMP”) active pharmaceutical ingredient (API) to meet our Buntanetap clinical study supply demands. We have also engaged a backup API manufacturing contractor, with primary operations in China. We have an agreement with a local U.S. supplier for the encapsulating, packaging, and stability of the clinical trial material. These arrangements will allow us to enter large and long-term advanced clinical studies. We have only limited supply agreements in place with respect to Buntanetap and our product candidates, and these arrangements do not extend to commercial supply. We do not have long term committed arrangements with respect to Buntanetap, any of our other product candidates, or other materials.

## **Government Regulation**

The FDA and comparable regulatory authorities in state and local jurisdictions and in other countries impose substantial and burdensome requirements upon companies involved in the clinical development, manufacture, marketing and distribution of drugs, such as those we are developing. These agencies and other federal, state and local entities regulate, among other things, the research and development, testing, manufacture, quality control, safety, effectiveness, labeling, storage, record keeping, approval, advertising and promotion, distribution, post-approval monitoring and reporting, sampling and export and import of our product candidates.

### ***U.S. Government Regulation of Drug Products***

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

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

- Completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA’s good laboratory practice regulations.
- Submission to the FDA of an IND, which must become effective before human clinical trials may begin.
- Approval by an independent institutional review board (“IRB”), at each clinical site before each trial may be initiated.
- Performance of adequate and well-controlled human clinical trials in accordance with good clinical practice (“GCP”), requirements to establish the safety and efficacy of the proposed drug product for each indication.
- Submission to the FDA of an NDA.
- Satisfactory completion of an FDA advisory committee review, if applicable.
- Satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with cGMP requirements and to assure that the facilities, methods and controls are adequate to preserve the drug’s identity, strength, quality and purity.
- Satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of the clinical data.
- Payment of user fees and securing FDA approval of the NDA.

- Compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy (“REMS”) and the potential requirement to conduct post-approval studies.

### ***Preclinical Studies***

Preclinical studies include laboratory evaluation of product chemistry, toxicity and formulation, as well as animal studies to assess potential safety and efficacy. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data and any available clinical data or literature, among other things, to the FDA as part of an IND. Some preclinical testing may continue even after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the clinical trial on a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to initiate.

### ***Clinical Trials***

Clinical trials involve the administration of the investigational new drug to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, an IRB at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it initiates at that institution. Information about certain clinical trials must be submitted within specific timeframes to the NIH for public dissemination on [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

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

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

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur.

### ***Special FDA Expedited Review and Approval Programs***

The FDA has various programs, including fast track designation, accelerated approval, priority review, and breakthrough therapy designation, which are intended to expedite or simplify the process for the development and FDA review of drugs that are intended for the treatment of serious or life-threatening diseases or conditions and demonstrate the potential to address unmet medical needs. The purpose of these programs is to provide important new drugs to patients earlier than under standard FDA review procedures.

To be eligible for a fast-track designation, the FDA must determine, based on the request of a sponsor, that a product is intended to treat a serious or life-threatening disease or condition and demonstrates the potential to address an unmet medical need. The FDA will determine that a product will fill an unmet medical need if it will provide a therapy where none exists or provide a therapy that may be potentially superior to existing therapy based on efficacy or safety factors. The FDA may review sections of the NDA for a fast-track product on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the

submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the NDA.

The FDA may give a priority review designation to drugs that offer major advances in treatment or provide a treatment where no adequate therapy exists. A priority review means that the goal for the FDA to review an application is six months, rather than the standard review of ten months under current PDUFA guidelines. Under the current PDUFA agreement, these six- and ten-month review periods are measured from the “filing” date rather than the receipt date for NDAs for new molecular entities, which typically adds approximately two months to the timeline for review and decision from the date of submission. Most products that are eligible for fast-track designation are also likely to be considered appropriate to receive a priority review.

In addition, products tested for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may be eligible for accelerated approval and may be approved on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (“IMM”) that is reasonably likely to predict an effect on IMM or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require a sponsor of a drug receiving accelerated approval to perform post-marketing studies to verify and describe the predicted effect on IMM or other clinical endpoint, and the drug may be subject to accelerated withdrawal procedures.

Moreover, under the provisions of the Food and Drug Administration Safety and Innovation Act passed in July 2012, a sponsor can request designation of a product candidate as a “breakthrough therapy.” A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening 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. Drugs designated as breakthrough therapies are also eligible for accelerated approval. The FDA must take certain actions, such as holding timely meetings and providing advice, intended to expedite the development and review of an application for approval of a breakthrough therapy. At the completion of our two Phase 2 trials, one in PD and one in AD, Annovis will petition the FDA to classify Buntanetap as a breakthrough therapy.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened. We may explore some of these opportunities for our product candidates as appropriate.

### ***Orphan Drug Designation and Exclusivity***

Under the Orphan Drug Act, the FDA may designate a drug product as an “orphan drug” if it is intended to treat a rare disease or condition (generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for treatment of the disease or condition will be recovered from sales of the product). A company must request orphan product designation before submitting an NDA. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product with orphan status receives the first FDA approval for a disease or condition, the product generally will be receiving orphan product exclusivity. Orphan product exclusivity means that the FDA may not approve any other applications for the same product for the same indication for seven years, except in certain limited circumstances. If a drug or drug product designated as an orphan product ultimately receives marketing approval for an indication broader than what was designated in its orphan product application, it may not be entitled to exclusivity. Orphan exclusivity will not bar approval of another product under certain circumstances, including if a subsequent product with the same active ingredient for the same indication is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand. Further, the FDA may approve more than one product for the same orphan indication or disease if the products contain different active ingredients. Moreover, competitors may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity.

## ***Marketing Approval and Post-Approval Requirements***

Assuming successful completion of the required clinical testing, the results of the preclinical and clinical studies, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. In most cases, the submission of an NDA is subject to a substantial application user fee. Under the Prescription Drug User Fee Act ("PDUFA") guidelines that are currently in effect, the FDA has a goal of ten months from the date of "filing" of a standard NDA, for a new molecular entity to review and act on the submission. This review typically takes twelve months from the date the NDA is submitted to FDA because the FDA has approximately two months to make a "filing" decision.

The FDA also may require submission of a REMS plan to ensure that the benefits of the drug outweigh its risks. The REMS plan could include medication guides, physician communication plans, assessment plans, and/or elements to assure safe use, such as restricted distribution methods, patient registries, or other risk minimization tools.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are sufficiently complete to permit substantive review. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA reviews an NDA to determine, among other things, whether the drug is safe and effective and whether the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product's continued safety, quality and purity.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. Additionally, before approving an NDA, the FDA may inspect one or more clinical trial sites to assure compliance with GCP requirements.

The FDA may refer an application for a novel drug to an advisory committee. While the FDA is not bound by the recommendations of an advisory committee, it considers such recommendations carefully when making decisions.

After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter, or, in some cases, a complete response letter. A complete response letter generally contains a statement of specific conditions that must be met in order to secure final approval of the NDA and may require additional clinical or preclinical testing for the FDA to reconsider the application. If and when those conditions have been met to the FDA's satisfaction, the FDA will typically issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications.

Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution and use restrictions or other risk management mechanisms under a REMS.

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

- Restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls.
- Fines, warning letters or holds on post-approval clinical trials.
- Refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product approvals.

- Product seizure or detention, or refusal to permit the import or export of products.
- Injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs or devices 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.

### ***U.S. Coverage and Reimbursement***

Significant uncertainty exists as to the coverage and reimbursement status of our lead product candidate, Buntanetap, or any other for which we may seek regulatory approval. Sales in the U.S. will depend in part on the availability of adequate financial coverage and reimbursement from third-party payors, which include government health programs such as Medicare, Medicaid, TRICARE and the Veterans Administration, as well as managed care organizations and private health insurers. Prices at which we or our customers seek reimbursement for our product candidates can be subject to challenge, reduction or denial by payors.

The process for determining whether a payor will provide coverage for a product is typically 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 the FDA-approved products for a particular indication. Also, third-party payors may refuse to include a branded drug on their formularies or otherwise restrict patient access to a branded drug when a less costly generic equivalent or another alternative is available. Medicare Part D, Medicare's outpatient prescription drug benefit, contains protections to ensure coverage and reimbursement for oral oncology products, and all Part D prescription drug plans are required to cover substantially all oral anti-cancer agents. However, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be available. Private payors often rely on the lead of the governmental payors in rendering coverage and reimbursement determinations. Sales of Buntanetap or any other product candidates will therefore depend substantially on the extent to which the costs of our products will be paid by third-party payors. Achieving favorable coverage and reimbursement from the Centers for Medicare and Medicaid Services ("CMS") and/or the Medicare Administrative Contractors is typically a significant gating issue for successful introduction of a new product.

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 marketing, we may need to conduct studies in order to demonstrate the medical necessity and cost-effectiveness of any products, which would be in addition to the costs expended to obtain regulatory approvals. Third-party payors may not consider our product candidates to be medically necessary or cost-effective compared to other available therapies, or the rebate percentages required to secure favorable coverage may not yield an adequate margin over cost or may not enable us to maintain price levels sufficient to realize an appropriate return on our investment in drug development.

### ***U.S. Healthcare Fraud and Abuse Laws and Compliance Requirements***

We are 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 and marketing 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 operations include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from soliciting, receiving, offering or paying remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation of, an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs. The term "remuneration" has been broadly interpreted to include anything of value;
- federal false claims and civil monetary penalties laws, including the federal civil False Claims Act, which prohibits anyone from, among other things, knowingly presenting, or causing to be presented, for payment to federal programs (including Medicare and Medicaid) claims for items or services that are false or fraudulent;

- provisions of the U.S. federal Health Insurance Portability and Accountability Act of 1996 (“HIPAA”), which created new federal criminal statutes that prohibit, among other things, knowingly and willfully executing a scheme to defraud any healthcare benefit program or making false statements in connection with the delivery of or payment for healthcare benefits, items or services. In addition, HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, impose certain requirements relating to the privacy, security and transmission of individually identifiable health information; and
- the federal Physician Payment Sunshine Act requirements, under the Patient Protection and Affordable Care Act, which require manufacturers of certain drugs and biologics to track and report to CMS payments and other transfers of value they make to U.S. physicians and teaching hospitals as well as physician ownership and investment interests in the manufacturer.

### ***Regulation Outside the United States***

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

To market our future products in the European Economic Area (“EEA”), which is comprised of the 28 Member States of the EU plus Norway, Iceland and Liechtenstein, and many other foreign jurisdictions, we must obtain separate regulatory approvals. More concretely, in the EEA, medicinal products can only be commercialized after obtaining a Marketing Authorization (“MA”). There are two types of MAs:

- The Community MA, which is issued by the European Commission through the Centralized Procedure, based on the opinion of the Committee for Medicinal Products for Human Use of the European Medicines Agency (“EMA”) and which is valid throughout the entire territory of the EEA. The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products and medicinal products indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and viral diseases. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU; and
- National MAs, which are issued by the competent authorities of the Member States of the EEA and only cover their respective territory, are available for products not falling within the mandatory scope of the Centralized Procedure. Where a product has already been authorized for marketing in a Member State of the EEA, this National MA can be recognized in another Member State through the Mutual Recognition Procedure. If the product has not received a National MA in any Member State at the time of application, it can be approved simultaneously in various Member States through the Decentralized Procedure.

Under the above-described procedures, before granting the MA, the EMA or the competent authorities of the Member States of the EEA assess the risk-benefit balance of the product based on scientific criteria concerning its quality, safety and efficacy.

### ***Data and Marketing Exclusivity***

In the EEA, new products authorized for marketing, or reference products, qualify for eight years of data exclusivity and an additional two years of market exclusivity upon marketing authorization. The data exclusivity period prevents generic or biosimilar applicants from relying on the pre-clinical and clinical trial data contained in the dossier of the reference product when applying for a generic or biosimilar marketing authorization in the EU during a period of eight years from the date on which the reference product was first authorized in the EU. The market exclusivity period prevents a successful generic or biosimilar applicant from commercializing its product in the EU until 10 years have elapsed from the initial authorization of the reference product in the EU. The 10-year market exclusivity period can be extended to a maximum of eleven years if, during the first eight years of those 10 years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies.

## ***Orphan Drug Designation***

In the EEA, a medicinal product can be designated as an orphan drug if its sponsor can establish that the product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the EU when the application is made, or that the product is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that the marketing of the drug in the EU would generate sufficient return to justify the necessary investment in development. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the EU or, if such method exists, the drug will be of significant benefit to those affected by that condition.

In the EEA, an application for designation as an orphan product can be made any time prior to the filing of an application for approval to market the product. Marketing authorization for an orphan drug leads to a ten-year period of market exclusivity. During this market exclusivity period, the EMA or the member state competent authorities, cannot accept another application for a marketing authorization, or grant a marketing authorization, for a similar medicinal product for the same indication. The period of market exclusivity is extended by two years for medicines that have also complied with an agreed PIP.

This period may, however, be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan drug designation, for example because the product is sufficiently profitable not to justify market exclusivity. Market exclusivity can be revoked only in very selected cases, such as consent from the marketing authorization holder, inability to supply sufficient quantities of the product, demonstration of “clinical superiority” by a similar medicinal product, or, after a review by the Committee for Orphan Medicinal Products, requested by a member state in the fifth year of the marketing exclusivity period (if the designation criteria are believed to no longer apply). Medicinal products designated as orphan drugs are eligible for incentives made available by the EU and its Member States to support research into, and the development and availability of, orphan drugs.

## **Human Capital Resources**

As of February 2023, we had five full-time employees. We also utilize the services of twelve consultants. We also contract with additional consultants and third parties for the conduct of certain clinical development, accounting and administrative activities. We are in the process of hiring additional employees as we advance in our clinical trial program. None of our employees are represented by labor unions or covered by collective bargaining agreements. We consider our relationship with our employees to be good.

Our human capital resources objectives include, as applicable, identifying, recruiting, retaining, training, incentivizing, and integrating our existing and new employees, advisors and consultants. We offer competitive compensation packages. We incentivize high performers through an annual bonus program based on our performance for which all employees are eligible. We also offer equity incentive plans, the purpose of which are to attract, retain and reward personnel through the granting of stock-based compensation awards in order to increase stockholder value and the success of our company by motivating team members to perform to the best of their abilities and achieve our objectives.

## **Corporate Information**

We were incorporated in Delaware in 2008. Our principal executive offices are located at 1055 Westlakes Drive, Suite 300, Berwyn, PA 19312 and our telephone number is (610)727 3913. Our website address is [www.annovisbio.com](http://www.annovisbio.com). The inclusion of our website address is, in each case, intended to be an inactive textual reference only and not an active hyperlink to our website. The information contained in, or that can be accessed through, our website is not part of this Annual Report on Form 10-K.



## Item 1A. Risk Factors

### Risks Related to Our Financial Position and Need for Additional Capital

***Because our auditor has issued a going concern opinion regarding our company, there is an increased risk associated with an investment in our company.***

As of December 31, 2022 we had cash and cash equivalents of \$28,377,693, and we have continually operated at a loss with an accumulated deficit of \$54,054,744 as of December 31, 2022. We have not attained profitable operations and are dependent upon obtaining financing to continue operations for the next twelve months from the date of these financial statements. Our future is dependent upon our ability to obtain financing or upon future profitable operations. We reserve the right to seek additional funds through public/private placements of our common stock and/or through debt financing. Our ability to raise additional financing is unknown. For these reasons, our auditors stated in their report that they have substantial doubt we will be able to continue as a going concern.

***We have incurred significant net losses since inception and anticipate that we will continue to incur net losses for the foreseeable future. We are not currently profitable, and we may never achieve or sustain profitability.***

Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. We are a clinical stage biopharmaceutical company with a limited operating history and have incurred losses since our formation. We incurred net losses of \$25,328,567 and \$14,487,132 for the years ended December 31, 2022 and 2021, respectively. As of December 31, 2022, we had an accumulated deficit of \$54,054,744. We have not commercialized any products and have never generated revenue from the commercialization of any product. To date, we have devoted most of our financial resources to research and development, including our preclinical and clinical work, and to intellectual property.

We expect to incur significant additional operating losses for the next several years, at least, as we advance Buntanetap and any other product candidates through clinical development, complete clinical trials, seek regulatory approval and commercialize the drug or any other product candidates, if approved. The costs of advancing product candidates into each clinical phase tend to increase substantially over the duration of the clinical development process. Therefore, the total costs to advance any of our product candidates to marketing approval in even a single jurisdiction will be substantial. Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to begin generating revenue from the commercialization of any products or achieve or maintain profitability. Our expenses will also increase substantially if and as we:

- commence our Phase 3 trials in AD and PD, or conduct clinical trials for any other product candidates;
- scale-up cGMP drug supply manufacturing and complete necessary work to support an NDA for Buntanetap in AD or in PD;
- are required by the FDA to complete additional toxicological/pharmacological studies to support an NDA for Buntanetap in AD or in PD;
- are required by the FDA to complete multiple Phase 3 trials to support an NDA for Buntanetap in AD or in PD;
- establish a sales, marketing and distribution infrastructure to commercialize our drug, if approved, and for any other product candidates for which we may obtain marketing approval;
- maintain, expand and protect our intellectual property portfolio;
- hire additional clinical, scientific and commercial personnel;
- add operational, financial and management information systems and personnel, including personnel to support our product development and future commercialization efforts, as well as to support our requirements as a public reporting company; and

- acquire or in-license or invent other product candidates or technologies.

Furthermore, our ability to successfully develop, commercialize and license any product candidates and generate product revenue is subject to substantial additional risks and uncertainties, as described under “—Risks Related to Development, Clinical Testing, Manufacturing and Regulatory Approval” and “—Risks Related to Commercialization.” This will require us to be successful in a range of challenging activities, including completing clinical trials and preclinical studies of Buntanetap and any other product candidates, acquiring additional product candidates, obtaining regulatory approval for Buntanetap and any other product candidates, and manufacturing, marketing, and selling any products for which we may obtain regulatory approval. We are only in the preliminary stages of most of these activities. As a result, we expect to continue to incur net losses and negative cash flows for the foreseeable future. These net losses and negative cash flows have had, and will continue to have, an adverse effect on our stockholders’ equity and working capital. The amount of our future net losses will depend, in part, on the rate of future growth of our expenses and our ability to generate revenues. If we are unable to develop and commercialize one or more product candidates, either alone or through collaborations, or if revenues from any product that receives marketing approval are insufficient, we will not achieve profitability. Even if we do achieve profitability, we may not be able to sustain profitability or meet outside expectations for our profitability. If we are unable to achieve or sustain profitability or to meet outside expectations for our profitability, the value of our company will be materially and adversely affected. Furthermore, this could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product candidates, achieve our strategic objectives or even continue our operations. A decline in the value of our company could also cause you to lose all or part of your investment.

***We will require substantial additional capital to fund our operations, and if we fail to obtain necessary financing, we may not be able to complete the development and commercialization of Buntanetap.***

The development of biopharmaceutical product candidates is capital-intensive. Our operations have consumed substantial amounts of cash since inception. We expect to continue to spend substantial amounts to advance the clinical development of Buntanetap. If we obtain regulatory approval for Buntanetap or any other product candidates, we also expect to incur significant commercialization expenses related to product manufacturing, marketing, sales, and distribution. We will require additional capital for the further development and potential commercialization of Buntanetap and may also need to raise additional funds sooner to pursue a more accelerated development of Buntanetap. Because the outcome of any clinical trial or preclinical study is highly uncertain, we cannot reliably estimate the actual amount of financing necessary to successfully complete the development and commercialization of Buntanetap or any other product candidates. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

Based on our current operating plan, we believe that our current cash and cash equivalents and funding from existing grants will enable us to fund our operating expenses and capital expenditure requirements until the fourth quarter of 2023. We have based this estimate on assumptions that may prove to be wrong, and we could deploy our available capital resources sooner than we currently expect. Our operating plans and other demands on our cash resources may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned. Our current cash and cash equivalents and funding from existing grants may not be sufficient to complete development of Buntanetap or any other product candidates, and we will require substantial capital in order to advance Buntanetap or any other product candidates through clinical trials, regulatory approval and commercialization. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. Our ability to raise additional funds may be adversely impacted by potential worsening global economic conditions and the disruptions to, and volatility in, the credit and financial markets in the United States and worldwide resulting from factors that include but are not limited to, inflation, the conflict between Russia and Ukraine and other factors, 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 capital when needed or on attractive terms, we could be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts, or even cease operations. We expect to finance our cash needs through public or private equity or debt financings or other capital sources, including potential collaborations, licenses and other similar arrangements. In addition, we may seek additional capital due to favorable market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. Attempting to secure additional

financing may divert our management from our day-to-day activities, which may adversely affect our ability to develop Buntanetap or any other product candidates.

Our future funding requirements, both near and long-term, will depend on many factors, including, but not limited to:

- the initiation, progress, timing, costs and results of preclinical studies and clinical trials, including patient enrollment in such trials, for Buntanetap or any other future product candidates;
- the clinical development plans we establish for Buntanetap and any other future product candidates, including any modifications to clinical development plans based on feedback that we may receive from regulatory authorities;
- the number and characteristics of product candidates that we discover or in-license and develop;
- the outcome, timing and cost of regulatory meetings and reviews by the FDA and comparable foreign regulatory authorities, including the potential for the FDA or comparable foreign regulatory authorities to require that we perform more studies than those that we currently expect;
- the requirements of regulatory authorities in any additional jurisdictions in which we may seek approval for Buntanetap and any future product candidates and our anticipated timing for seeking approval in such jurisdictions;
- the costs of filing, prosecuting, defending and enforcing any patent claims and maintaining and enforcing other intellectual property and proprietary rights;
- the effects of competing technological and market developments;
- the costs associated with hiring additional personnel and consultants as our business grows, including additional executive officers and clinical development, regulatory, CMC quality and commercial personnel;
- the costs and timing of the implementation of commercial-scale manufacturing activities, if any product candidate is approved, including as a result of inflation, any supply chain issues or component shortages;
- the costs and timing of establishing sales, marketing and distribution capabilities for any product candidates for which we may receive regulatory approval;
- our ability to achieve sufficient market acceptance, coverage and adequate reimbursement from third-party payors and adequate market share and revenue for any approved products;
- the terms and timing of establishing and maintaining collaborations, licenses and other similar arrangements;
- the costs associated with any products or technologies that we may in-license or acquire; and
- any delays and cost increases that may result from the COVID-19 or any future pandemic.

Conducting clinical trials and preclinical studies and potentially identifying future product candidates is a time consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain regulatory approval and commercialize Buntanetap or any future product candidates. If approved, Buntanetap and any future product candidates may not achieve commercial success. Our commercial revenue, if any, will initially be derived from sales of Buntanetap, which we do not expect to be commercially available for many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all. If we are unable to expand our operations or otherwise capitalize on our business opportunities due to a lack of capital, our ability to become profitable will be compromised.

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

Until such time, if ever, as we can generate substantial revenue, we may finance our cash needs through a combination of equity offerings, debt financings, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements or other sources. We do not currently have any committed external source of funds. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe that we have sufficient funds for our current or future operating plans.

To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. Such restrictions could adversely impact our ability to conduct our operations and execute our business plan. If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may be required to relinquish valuable rights to our technologies, intellectual property, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us and/or that may reduce the value of our common stock. If we are unable to raise additional funds through equity or debt financings when needed, we would be required to delay, limit, reduce or terminate product candidate development or future commercialization efforts, or grant rights to develop and market product candidates that we might otherwise prefer to develop and market ourselves, or on less favorable terms than we would otherwise choose.

***We have limited operating history and no history of commercializing pharmaceutical products.***

We were established and began operations in 2008. Our operations to date have been primarily focused on conducting preclinical and clinical studies. We have not yet demonstrated the ability to successfully complete a large-scale, pivotal clinical trial, obtain marketing approval, manufacture a commercial scale product, arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Consequently, any predictions made about our future success or viability may not be as accurate as they could be if we had a history of successfully developing and commercializing biopharmaceutical products. In addition, as a business with a limited operating history, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors.

As we continue to build our business, we expect our financial condition and operating results may fluctuate significantly from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. Accordingly, reliance should not be placed upon the results of any particular quarterly or annual period as indications of future operating performance.

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

In general, under Section 382 of the U.S. Internal Revenue Code of 1986, as amended (the “Code”), a corporation that undergoes an “ownership change” is subject to limitations on its ability to use its pre-change net operating loss carryforwards (“NOLs”) to offset future taxable income. Due to previous ownership changes, our ability to use our NOLs could be limited by Section 382 of the Code. Future changes in our stock ownership, some of which are outside of our control, could result in an ownership change under Section 382 of the Code. Furthermore, our ability to use NOLs of companies that we may acquire in the future may be subject to limitations. For these reasons, we may not be able to use a material portion of the NOLs, even if we attain profitability in the future.

***Inflation could adversely affect our business and results of operations.***

While inflation in the United States has been relatively low in recent years, during 2021 and 2022, the economy in the United States encountered a material level of inflation. The impact of COVID-19, geopolitical developments such as the Russia-Ukraine conflict and global supply chain disruptions continue to increase uncertainty in the outlook of near-term and long-term economic activity, including whether inflation will continue and how long, and at what rate. Increases in inflation raise our costs for commodities, labor, materials and services and other costs required to grow and operate our business, and failure to secure these on reasonable terms may adversely impact our financial condition. Additionally, increases in inflation, along with the uncertainties

surrounding COVID-19, geopolitical developments and global supply chain disruptions, have caused, and may in the future cause, global economic uncertainty and uncertainty about the interest rate environment, which may make it more difficult, costly or dilutive for us to secure additional financing. A failure to adequately respond to these risks could have a material adverse impact on our financial condition, results of operations or cash flows.

***Unstable market and economic conditions may have serious adverse consequences on our business, financial condition and stock price.***

The global credit and financial markets have recently 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. The financial markets and the global economy may also be adversely affected by the current or anticipated impact of military conflict, including the conflict between Russia and Ukraine, terrorism or other geopolitical events. Sanctions imposed by the United States and other countries in response to such conflicts, including the one in Ukraine, may also adversely impact the financial markets and the global economy, and any economic countermeasures by the affected countries or others could exacerbate market and economic instability. There can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions will not occur. Our general business strategy may be adversely affected by any such economic downturn, volatile business environment or continued unpredictable and unstable market conditions. If the current equity and credit markets deteriorate, it may make any necessary debt or equity financing more difficult, more costly and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and stock price and could require us 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, or on less favorable terms than we would otherwise choose. In addition, if one or more of our current service providers, manufacturers and other partners may not survive an economic downturn, which could directly affect our ability to attain our clinical development goals on schedule and on budget.

#### **Risks Related to Development, Clinical Testing, Manufacturing and Regulatory Approval**

***We are heavily dependent on the success of Buntanetap, our most advanced product candidate, which is still under clinical development, and if this drug does not receive regulatory approval or is not successfully commercialized, our business will be materially harmed.***

We do not have any products that have gained regulatory approval. Currently, our lead clinical stage product candidate is Buntanetap. As a result, our business is entirely dependent on our ability to successfully complete clinical development of, obtain regulatory approval for, and, if approved, successfully commercialize Buntanetap in a timely manner. This may make an investment in our company riskier than similar companies that have multiple product candidates in active development and may be able to better sustain the delay or failure of a lead product candidate. We cannot commercialize Buntanetap in the United States without first obtaining regulatory approval from the FDA; similarly, we cannot commercialize Buntanetap outside of the United States without obtaining regulatory approval from comparable foreign regulatory authorities. Before obtaining regulatory approvals for the commercial sale of Buntanetap for a target indication, we must demonstrate with substantial evidence gathered in preclinical studies and clinical trials, generally including two adequate and well-controlled clinical trials, and, with respect to approval in the United States, to the satisfaction of the FDA, that Buntanetap is safe and effective for use for that target indication and that the manufacturing facilities, processes and controls are adequate. If the FDA is not satisfied with the quantity and nature of the data we collect, we may be forced to undertake additional preclinical studies or clinical trials to obtain regulatory approval, which will lead to delays in our clinical development plans and cause us to incur additional costs, both of which may have a material adverse effect on our business. Even if Buntanetap were to successfully obtain approval from the FDA and comparable foreign regulatory authorities, any approval might contain significant limitations related to use restrictions for specified age groups, warnings, precautions or contraindications, or may be subject to burdensome post-approval study or risk management requirements. If we are unable to obtain regulatory approval for Buntanetap in one or more jurisdictions, or any approval contains significant limitations, we may not be able to obtain sufficient funding or generate sufficient revenue to continue the development of any other product candidate that we may in-license, develop or acquire in the future. Furthermore, even if we obtain regulatory approval for Buntanetap, we will still need to develop a commercial organization, establish commercially viable pricing and obtain approval for adequate reimbursement from third-party and government payors. If we are unable to successfully commercialize Buntanetap, we may not be able to earn sufficient revenue to continue our business.

***If we are not successful in discovering, developing and commercializing additional product candidates, our ability to expand our business and achieve our strategic objectives would be impaired.***

Research programs to identify product candidates require substantial technical, financial and human resources, whether or not any product candidates are ultimately identified. Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for many reasons, including the following:

- competitors may develop alternatives that render any product candidates we develop obsolete;
- any product candidates we develop may nevertheless be covered by third parties' patents or other exclusive rights;
- a product candidate may be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective or otherwise does not meet applicable regulatory criteria;
- a product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all; and
- a product candidate may not be accepted as safe and effective by physicians, patients, the medical community or third-party payors.

We have limited financial and personnel resources and, as a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater market potential. Our resource allocation decisions may cause it to fail to capitalize on viable commercial drugs or profitable market opportunities. If we do not accurately evaluate the commercial potential or target market for a particular product, we may relinquish valuable rights to that product through collaboration, licensing or other royalty arrangements in circumstances under which it would have been more advantageous for us to retain sole development and commercialization rights to such product. If we are unsuccessful in identifying and developing additional product candidates or are unable to do so, our business, results of operations, cash flows, financial condition and/or prospects may be materially and adversely affected.

***Business disruptions, including but not limited to those associated with widespread health emergencies, could harm our ability to complete or could materially delay our clinical trials, as well as cause disruptions to the FDA and other governmental authorities.***

Our operations and the operations of our suppliers, contract research organizations ("CROs"), hospitals, clinical trial sites, regulators, consultants and other third parties with whom we conduct business could be subject to earthquakes, power shortages, telecommunications or infrastructure failures, cybersecurity incidents, physical security breaches, water shortages, floods, hurricanes, typhoons, blizzards and other extreme weather conditions, fires, and other natural or manmade disasters or business interruptions, for which we are predominantly self-insured. We rely on third-party manufacturers or suppliers to produce Buntanetap and its components and on CROs and clinical sites to conduct our clinical trials, and do not have a redundant source of supply for all components of our product candidate. Our ability to obtain clinical or, if approved, commercial, supplies of Buntanetap or any future product candidates could be disrupted if the operations of these suppliers were affected by a man-made or natural disaster or other business interruption, and our ability to commence, conduct or complete our clinical trials in a timely manner could be similarly adversely affected by any of the foregoing. The occurrence of any of these business disruptions could seriously harm our operations and financial condition and increase our costs and expenses.

Furthermore, the emergence of widespread health emergencies or pandemics, such as COVID-19, could lead to quarantines, business shutdowns, labor shortages, disruptions to the healthcare system, and overall economic instability. If the suppliers, CROs, hospitals, clinical trial sites, regulators, consultants and other third parties with whom we conduct business were to experience shutdowns or other business disruptions, our ability to enroll patients and conduct our clinical trials in the manner and on the timelines presently planned could be materially and negatively impacted. As an example, in March 2020, the clinical trial sites participating in our Phase 1/2 trial in AD patients in collaboration with the ADCS temporarily suspended enrollment of new patients because of the ongoing COVID-19 pandemic and patient recruitment and treatment were completed later than anticipated. In addition, due to restrictions related to COVID-19 during 2020, we experienced delays in opening clinical trial sites for our AD/PD Trials. The extent to which other future emerging widespread health emergencies or pandemics could have a material impact on our clinical trials is dependent on the spread of the disease and government and healthcare system responses to such spread, which are presently unpredictable.

The COVID-19 pandemic and any future epidemic or pandemic disease outbreak could also potentially further affect the business of the FDA, EMA or other regulatory authorities, which could result in delays in meetings related to our planned clinical trials. The COVID-19 pandemic and mitigation measures have had and may continue to have, and any future epidemic disease outbreak may have, an adverse impact on global economic conditions which could have an adverse effect on our business and financial condition, including impairing our ability to raise capital when needed. The extent to which the COVID-19 pandemic impacts our results will depend on future developments that are highly uncertain and cannot be predicted, including new information that may emerge concerning the severity of the virus, including the identification of new variants, the rate of vaccine administration, and the actions to contain its impact.

***Clinical trials are expensive, time-consuming and difficult to design and implement, and involve an uncertain outcome.***

Clinical development is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. Because the results of preclinical studies and early clinical trials are not necessarily predictive of future results, Buntanetap and our other product candidates may not have favorable results in later preclinical and clinical studies or receive regulatory approval. The historical failure rate for product candidates in our industry is high, particularly in the earlier stages of development. Furthermore, product candidates in later stages of clinical trials may fail to show the desired safety and efficacy characteristics despite having progressed through preclinical studies and initial clinical trials. We may experience delays in initiating and completing any clinical trials that we intend to conduct, and we do not know whether planned clinical trials will begin on time, need to be redesigned, enroll patients on time or be completed on schedule, or at all. Clinical trials can be delayed for a variety of reasons, including delays related to:

- the FDA or comparable foreign regulatory authorities disagreeing as to the design or implementation of our clinical studies;
- obtaining regulatory approval to commence a trial;
- reaching an agreement on acceptable terms with prospective CROs, and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- obtaining Institutional Review Board (“IRB”) approval at each site, or Independent Ethics Committee (“IEC”) approval at sites outside the United States;
- recruiting suitable patients to participate in a trial in a timely manner and in sufficient numbers;
- patients failing to complete a trial or return for post-treatment follow-up;
- imposition of a clinical hold by regulatory authorities, including as a result of unforeseen safety issues or side effects or failure of trial sites to adhere to regulatory requirements or follow trial protocols;
- clinical sites deviating from trial protocol or dropping out of a trial;
- addressing patient safety concerns that arise during the course of a trial;
- adding a sufficient number of clinical trial sites; or
- manufacturing sufficient quantities of product candidate for use in clinical trials.

We could also encounter delays if a clinical trial is suspended or terminated by us, the IRBs or IECs of the institutions in which such trials are being conducted, the Data Safety Monitoring Board (“DSMB”), for such trial or the FDA or other regulatory authorities. Such authorities may impose such a suspension or termination due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a drug, changes in governmental regulations or administrative actions or lack of

adequate funding to continue the clinical trial. Furthermore, we rely on CROs and clinical trial sites to ensure the proper and timely conduct of our clinical trials and, while we have agreements governing their committed activities, we have limited influence over their actual performance, as described in “—Risks Related to Our Dependence on Third Parties.”

***The regulatory approval processes of the FDA and comparable foreign authorities are lengthy, time consuming and inherently unpredictable, and if we are ultimately unable to obtain regulatory approval for Buntanetap or any other product candidates, our business will be substantially harmed.***

The time required to obtain approval by the FDA and comparable foreign authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate’s clinical development and may vary among jurisdictions. We have not obtained regulatory approval for any product candidate and it is possible that we will never obtain regulatory approval for Buntanetap or any other product candidate. We are not permitted to market any of our product candidates in the United States until we receive regulatory approval of an NDA from the FDA. Approval from the FDA and comparable foreign authorities may be delayed or denied for a variety of reasons, including:

- we may be unable to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that a product candidate is safe and effective for its proposed indication;
- serious and unexpected drug-related side effects experienced by participants in our clinical trials or by individuals using drugs similar to our product candidates, or other products containing the active ingredient in our product candidates;
- negative or ambiguous results from our clinical trials or results that may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for approval;
- we may be unable to demonstrate that a product candidate’s clinical and other benefits outweigh its safety risks;
- the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical trials;
- the data collected from clinical trials of our product candidates may not be acceptable or sufficient to support the submission of an NDA or other submission or to obtain regulatory approval in the United States or elsewhere, and we may be required to conduct additional clinical trials;
- the FDA or comparable foreign authorities may disagree regarding the formulation, labeling and/or the specifications of our product candidates;
- the FDA or comparable foreign regulatory authorities may fail to approve or find deficiencies with the manufacturing processes or facilities of third-party manufacturers with which we contract for clinical and commercial supplies; and
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

Prior to obtaining approval to commercialize a product candidate in the United States or abroad, we must demonstrate with substantial evidence from well-controlled clinical trials, and to the satisfaction of the FDA or foreign regulatory agencies, that such product candidates are safe and effective for their intended uses. Results from preclinical studies and clinical trials can be interpreted in different ways. Even if we believe the preclinical or clinical data for our product candidates are promising, such data may not be sufficient to support approval by the FDA and other regulatory authorities. For diseases like AD and PD, the FDA has stated that one single Phase 3 trial is adequate for approval if it demonstrates robust and unquestionable efficacy. However, the circumstances under which a single adequate and controlled study can be used as the sole basis of demonstrating efficacy of a drug are exceptional.



The FDA or any foreign regulatory bodies can delay, limit or deny approval of our product candidates or require us to conduct additional preclinical or clinical testing or abandon a program for many reasons, including:

- the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials;
- the FDA or comparable foreign regulatory authorities may disagree with our safety interpretation of our drug;
- the FDA or comparable foreign regulatory authorities may disagree with our efficacy interpretation of our drug;
- the FDA or comparable foreign regulatory authorities may regard our CMC package as inadequate.

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

In addition, the FDA or the applicable foreign regulatory agency also may approve a product candidate for a more limited indication or patient population than we originally requested, and the FDA or applicable foreign regulatory agency may approve a product candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates.

***We have concentrated our research and development efforts on the treatment of AD and PD, diseases that have seen limited success in drug development. Further, Buntanetap is based on a new approach to treating AD and PD, which makes it difficult to predict the time and cost of development and subsequent obtaining of regulatory approval.***

Efforts by biopharmaceutical and pharmaceutical companies in treating AD and PD have seen limited success in drug development, and there are no FDA-approved disease modifying therapeutic options available for patients with AD and PD. As a result, the design and conduct of clinical trials of Buntanetap or any future product candidate may take longer, be more costly or be less effective as a result of the novelty of development in these diseases. We cannot be certain that our approach will lead to the development of approvable or marketable products. In some cases, we may use endpoints or methodologies that regulatory authorities may not consider to be clinically meaningful and that we may not continue to use in clinical trials or that we may determine after the initiation of the trial to no longer be an appropriate endpoint or methodology. Any such regulatory authority may require evaluation of additional or different clinical endpoints in our clinical trials or ultimately determine that these clinical endpoints do not support marketing approval. In addition, if we are required to use additional or different clinical endpoints by regulatory authorities, Buntanetap may not achieve or meet such clinical endpoints in our clinical trials. Even if a regulatory authority finds our clinical trial success criteria to be sufficiently validated and clinically meaningful, we may not achieve the pre-specified endpoint to a degree of statistical significance in any pivotal or other clinical trials we may conduct for our product candidate. Further, even if we do achieve the prespecified criteria, our trials may produce results that are unpredictable or inconsistent with the results of other efficacy endpoints in the trial. Regulatory authorities also could give overriding weight to other efficacy endpoints over a primary endpoint even if we achieve statistically significant results on that primary endpoint if we do not do so on our secondary efficacy endpoints. Regulatory authorities also weigh the benefits of a product against its risks and may view the efficacy results in the context of safety as not being supportive of approval.

The only drugs approved by the FDA to treat AD and PD to date address the diseases' symptoms. No new treatments have been approved for AD since 2003. From 2004 to 2022, phase 2 and 3 clinical trials for unique compounds with various mechanisms of action intended to combat AD had a development success rate of just 2%. AD drug candidates have the highest failure rate of nearly 100%, compared to 50% to 80% for all other drug candidates. As a result, the FDA has a limited set of products to rely on in evaluating Buntanetap. This could result in a longer than expected regulatory review process, increased expected development costs or the delay or prevention of commercialization of Buntanetap for the treatment of AD and PD. We cannot be sure that Buntanetap, or any other product candidate we develop, will ultimately prove to be safe and effective, scalable or profitable. Moreover, public perception of drug 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 prescribe novel treatments.

***Changes in methods of product candidate manufacturing or formulation may result in additional costs or delay.***

As product candidates progress through clinical trials to marketing approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods and formulation, are altered along the way in an effort to optimize safety, efficacy, yield and manufacturing batch size, minimize costs and achieve consistent quality and results. For example, the manufacturing process being used to produce clinical material for our planned clinical trials is different than that used in prior trials of Buntanetap. There can be no assurance that such changes will achieve these intended objectives. These changes and any future changes we may make to Buntanetap or any future product candidates may also cause such candidates to perform differently and affect the results of future clinical trials conducted with the altered materials. Such changes or related unfavorable clinical trial results could delay initiation or completion of additional clinical trials, require the conduct of bridging studies or clinical trials or the repetition of one or more studies or clinical trials, increase development costs, delay or prevent potential marketing approval and jeopardize our ability to commercialize Buntanetap or any future product candidates, if approved, and generate revenue.

***We may develop Buntanetap and future product candidates for use in combination with other therapies, which could expose us to additional regulatory risks.***

We may develop Buntanetap and future product candidates for use in combination with one or more other approved therapies for AD or PD. Even if any product candidate we develop were to receive marketing approval or be commercialized for use in combination with other existing therapies, we would continue to be subject to the risk that the FDA or comparable foreign regulatory authorities could revoke approval of the therapy used in combination with our product candidate or that safety, efficacy, manufacturing or supply issues could arise with these existing therapies. This could result in our own products being removed from the market or being less successful commercially.

Further, we will not be able to market and sell any product candidate we develop in combination with an unapproved AD or PD therapy for a combination indication if that unapproved therapy does not ultimately obtain marketing approval either alone or in combination with our product. In addition, unapproved AD and PD therapies face the same risks described with respect to our product candidates currently in development and clinical trials, including the potential for serious adverse effects, delay in their clinical trials and lack of FDA approval.

***Enrollment and retention of patients in clinical trials is an expensive and time-consuming process and could be made more difficult or rendered impossible by multiple factors outside our control.***

The timely completion of clinical trials in accordance with their protocols depends, among other things, on our ability to enroll a sufficient number of patients who remain in the study until its conclusion. We may encounter delays in enrolling, or be unable to enroll, a sufficient number of patients to complete any of our clinical trials, and even once enrolled, we may be unable to retain a sufficient number of patients to complete any of our trials. For example, during the COVID-19 pandemic, we had difficulties enrolling a sufficient number of patients for our clinical trials.

Patient enrollment and retention in clinical trials depends on many factors, including:

- the patient eligibility and exclusion criteria defined in the protocol;
- the size of the patient population required for analysis of the trial's primary endpoints;
- the nature and design of the trial protocol;
- the existing body of safety and efficacy data with respect to the product candidate;
- the proximity of patients to clinical sites;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience;

- clinicians' and patients' perceptions as to the potential advantages and risks of the product candidate being studied in relation to other available therapies, including any new drugs that may be approved for the indications we are investigating;
- competing clinical trials being conducted by other companies or institutions;
- our ability to obtain and maintain patient consents; and
- the risk that patients enrolled in clinical trials will drop out of the trials before completion.

Potential patients for any planned clinical trials may not be adequately diagnosed or identified with the diseases which we are targeting, which could adversely impact the outcomes of our trials and could have safety concerns for the potential patients. Additionally, other pharmaceutical companies targeting these same diseases are recruiting clinical trial patients from these patient populations, which may make it more difficult to fully enroll our clinical trials. We may not be able to initiate or continue clinical trials if we are unable to locate a sufficient number of eligible patients to participate in the clinical trials required by the FDA or comparable foreign regulatory authorities. In addition, the process of finding and recruiting patients may prove costly. The timing of our clinical trials depends, in part, on the speed at which we can recruit patients to participate in our trials, as well as completion of required follow-up periods. If patients are unwilling or unable to participate in our trials for any reason, including the existence of concurrent clinical trials for similar target populations, the availability of approved or authorized therapies, the effects of the COVID-19 pandemic, or the fact that enrolling in our trials may prevent patients from taking a different product, or we otherwise have difficulty enrolling a sufficient number of patients, the timeline for recruiting patients, conducting trials and obtaining regulatory approval of our product candidates may be delayed. Our inability to enroll a specified number of patients for any of our future clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether.

***Results of preclinical studies, early clinical trials or analyses may not be indicative of results obtained in later trials.***

The results of preclinical studies, early clinical trials or analyses of our product candidates may not be predictive of the results of later-stage clinical trials. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through preclinical studies and initial clinical trials. Furthermore, results of early clinical trials may differ from results of later clinical trials due to changes in patient population size. The clinical trials that we have completed to date included a limited patient population, and we may observe differences in the safety and efficacy of Buntanetap and our other product candidates as the patient population increases in size. Accordingly, the data that we have observed to date may not be reflective of ongoing and future clinical trial data. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. In addition, conclusions based on promising data from analyses of clinical results may be shown to be incorrect when implemented in prospective clinical trials. Even if our clinical trials for Buntanetap are completed as planned, we cannot be certain that their results will support the safety and efficacy sufficient to obtain regulatory approval.

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 development program, the approvability or commercialization of the particular product candidate or product and our company in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is based on what is typically extensive information, and others may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure. Any information we determine not to disclose may ultimately be deemed meaningful by others with respect to future decisions, conclusions, views, activities or otherwise regarding a particular product candidate or our business. If the interim, topline or preliminary data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, product candidates may be harmed, which could significantly harm our business prospects.

***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 further subject to audit and verification procedures that could result in material changes in the final data. Furthermore, undue reliance on interim analyses may be detrimental to our long-term clinical development plans, which could harm our business, operating results, prospects or financial condition.***

From time to time, we may publish interim “top-line” or preliminary data from our clinical studies, which is based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study. 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 evaluate all data fully and carefully. Preliminary or “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, interim and preliminary data should be viewed with caution until the final data are 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.

In addition, others, including regulatory authorities, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and our company in general. Moreover, 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 drug, product candidate or our business. If the interim “topline” or preliminary data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, Buntanetap and any future product candidates may be harmed, which could harm our business, operating results, prospects or financial condition.

Furthermore, interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available, or different conclusions or considerations may qualify such results once additional data have been received and fully evaluated. We intend to rely on interim data from our Phase 3 PD Study and Phase 2/3 AD Study to obtain feedback on our ongoing and planned AD and PD studies, and ultimately design future studies. Specifically, we plan to use the data from the Phase 3 PD Study interim analysis to design an 18-month long disease-modifying Phase 3 study in the same early PD patients, and intend to conduct a short 6-month study in advanced PD patients during the second half of the 18-month disease modifying Phase 3 study. Similarly, using the data from the Phase 2/3 AD Study interim analysis, we intend to design an 18-month disease modifying Phase 3 study in the same early AD patient population, and intend to conduct a short 6-month study in advanced AD patients during the second half of the 18-month disease modifying Phase 3 study. Such reliance on the Phase 3 PD Study and Phase 2/3 AD Study interim analyses could be detrimental to our long-term clinical development plans, as data available at the time of the built-in interim analyses could be materially different from the data that would be available if we completed a longer study, or a study with increased patient enrollment. Accordingly, if the interim data upon which we rely is later shown to be materially different from the final, complete study results, the basis upon which we set forth our development plans may be called into question and our ability to obtain approval for, and commercialize, Buntanetap may be harmed, which could harm our business, operating results, prospects or financial condition.

***Our product candidates may cause serious adverse events or undesirable side effects, which may delay or prevent marketing approval, or, if approved, require them to be taken off the market, require them to include safety warnings or otherwise limit their sales.***

As is the case with biopharmaceuticals generally, it is likely that there may be adverse side effects associated with Buntanetap or any future product candidates’ use. Serious adverse events or undesirable side effects caused by Buntanetap or any other product candidates could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other comparable foreign authorities. Results of any clinical trial we conduct could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. Patients treated with Buntanetap to date, at high doses have experienced adverse events that include nausea, vomiting and dizziness.

If unacceptable side effects arise in the development of our product candidates, we, the FDA or the IRBs at the institutions in which our studies are conducted, or the DSMB, if constituted for our clinical trials, could recommend a suspension or termination of our clinical trials, or the FDA or comparable foreign regulatory authorities could order us to cease further development of or deny approval of a product candidate for any or all targeted indications. In addition, drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete a trial or result in potential product liability claims. In addition, these side effects may not be appropriately recognized or managed by the treating medical staff. We expect to have to train medical personnel using our product candidates to understand the side effect profiles for our clinical trials and upon any commercialization of any of our product candidates. Inadequate training in recognizing or managing the potential side effects of our product candidates could result in patient injury or death. Any of these occurrences may harm our business, financial condition and prospects significantly.

Moreover, if Buntanetap or any future product candidates are associated with undesirable side effects in clinical trials or demonstrate characteristics that are unexpected, we may elect to abandon their development or limit their development to more narrow uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective, which may limit the commercial expectations for the product candidate if approved. We may also be required to modify our development and clinical trial plans based on findings in our ongoing clinical trials. Many product candidates that initially showed promise in early-stage testing have later been found to cause side effects that prevented further development of the product candidates.

It is possible that as we test Buntanetap or any future product candidates in larger, longer and more extensive clinical trials, including with different dosing regimens, or as the use of these product candidates becomes more widespread following any regulatory approval, more illnesses, injuries, discomforts and other adverse events than were observed in earlier trials, as well as new conditions that did not occur or went undetected in previous trials, may be discovered. If such side effects become known later in development or upon approval, if any, such findings may harm our business, financial condition and prospects significantly.

Additionally, if one or more of our product candidates receives marketing approval, and we or others later identify undesirable side effects caused by such products, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw approvals of such product;
- regulatory authorities may require additional warnings on the label, such as a “black box” warning or contraindication;
- additional restrictions may be imposed on the marketing of the particular product or the manufacturing processes for the product or any component thereof;
- we may be required to implement a REMS or create a medication guide outlining the risks of such side effects for distribution to patients;
- we could be sued and held liable for harm caused to patients;
- the product may become less competitive; and
- our reputation may suffer.

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

***The market opportunities for Buntanetap or any other product candidates, if approved, may be smaller than we anticipate, which could adversely affect our business, financial condition and results of operations.***

We expect to initially seek approval for Buntanetap for AD and PD in the U.S. The precise incidence and prevalence for the conditions we aim to address with Buntanetap or any future product candidates are unknown. Our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on a number of internal and third-party estimates. These estimates have been derived from a variety of sources, including the scientific literature, patient foundations and market research, and may prove to be incorrect. Further,

new trials may change the estimated incidence or prevalence of these indications. While we believe our assumptions and the data underlying our estimates are reasonable, we have not independently verified the accuracy of the third-party data on which we have based our assumptions and estimates, and these assumptions and estimates may not be correct and the conditions supporting our assumptions or estimates may change at any time, including as a result of factors outside our control, thereby reducing the predictive accuracy of these underlying factors. The total addressable market across all of the potential indications for Buntanetap and any future product candidates will ultimately depend upon, among other things, the diagnosis criteria included in the final label for each such product candidate which receives marketing approval for these indications, the availability of alternative treatments and the safety, convenience, cost and efficacy of such product candidates relative to such alternative treatments, acceptance by the medical community and patient access, drug pricing and reimbursement. The number of patients in the United States and other major markets and elsewhere may turn out to be lower than expected, patients may not be otherwise amenable to treatment with our product candidates or new patients may become increasingly difficult to identify or gain access to, all of which would adversely affect our business, financial condition and results of operations. Even if we obtain significant market share for any product candidate, if approved, if the potential target populations are small, we may never achieve profitability without obtaining marketing approval for additional indications.

***We have never obtained marketing approval for a product candidate and we may be unable to obtain, or may be delayed in obtaining, marketing approval for any of our product candidates. Further, even if marketing approval is obtained, we have no experience as a company in commercializing products.***

We have never obtained marketing approval for a product candidate. It is possible that the FDA may refuse to accept for substantive review any NDAs that we submit for our product candidates or may conclude after review of our data that our application is insufficient to obtain marketing approval of our product candidates. If the FDA does not accept or approve our NDAs for our product candidates, it may require that we conduct additional clinical, preclinical or manufacturing validation studies and submit that data before it will reconsider our applications. Depending on the extent of these or any other FDA-required studies, approval of any NDA that we submit may be delayed or may require us to expend more resources than we have available. It is also possible that additional studies, if performed and completed, may not be considered sufficient by the FDA to approve our NDAs.

Any delay in obtaining, or an inability to obtain, marketing approvals would prevent us from commercializing our product candidates, generating revenues and achieving and sustaining profitability. If any of these outcomes occur, we may be forced to abandon our development efforts for our product candidates, which could significantly harm our business.

Furthermore, we have no internal sales, marketing or distribution capabilities, nor have we commercialized a product. If Buntanetap or any future product candidates ultimately receives marketing approval, we must build a marketing and sales organization with technical expertise and supporting distribution capabilities to commercialize each such product in major markets, which will be expensive and time consuming, or collaborate with third parties that have direct sales forces and established distribution systems, either to augment our own sales force and distribution systems or in lieu of our own sales force and distribution systems. We have no prior experience as a company with the marketing, sale or distribution of biopharmaceutical products and there are significant risks involved in the building and managing of a sales organization, including our ability to hire, retain and incentivize qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel and effectively manage a geographically dispersed sales and marketing team. Any failure or delay in the development of our internal sales, marketing and distribution capabilities would adversely impact the commercialization of these products. We may not be able to enter into collaborations or hire consultants or external service providers to assist us in sales, marketing and distribution functions on acceptable financial terms, or at all. In addition, our product revenue and our profitability, if any, may be lower if we rely on third parties for these functions than if we were to market, sell and distribute any products that we develop ourselves. 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 products effectively. If we are not successful in commercializing our products, either on our own or through arrangements with one or more third parties, we may not be able to generate any future product revenue and we would incur significant additional losses.

***Even if we obtain FDA approval for Buntanetap or any other product candidates in the United States, we may never obtain approval for or commercialize Buntanetap or any other product candidates in any other jurisdiction, which would limit our ability to realize their full market potential.***

Our future growth may depend, in part, on our ability to develop and commercialize Buntanetap and any future product candidates in foreign markets. We are not permitted to market or promote any product candidate before we receive regulatory

approval from applicable regulatory authorities in foreign markets, and we may never receive such regulatory approvals for Buntanetap or any future product candidates. In order to market any products in any particular jurisdiction, we must establish and comply with numerous and varying regulatory requirements on a country-by-country basis regarding safety and efficacy. Approval by the FDA in the United States does not ensure approval by regulatory authorities in other countries or jurisdictions. However, the failure to obtain approval in one jurisdiction may negatively impact our ability to obtain approval elsewhere. In addition, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not guarantee regulatory approval in any other country.

Approval processes vary among countries and can involve additional product testing and validation and additional administrative review periods. Seeking foreign regulatory approval could result in difficulties and increased costs for us and require additional preclinical studies or clinical trials which could be costly and time consuming. Regulatory requirements can vary widely from country to country and could delay or prevent the introduction of our products in those countries. We do not have any product candidates approved for sale in any jurisdiction, including in international markets, and we do not have experience in obtaining regulatory approval in international markets. If we fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals, or if regulatory approvals in international markets are delayed, our target market will be reduced and our ability to realize the full market potential of any product we develop will be unrealized.

If we obtain regulatory approval of product candidates and ultimately commercialize our products in foreign markets, we would be subject to additional risks and uncertainties, including:

- different regulatory requirements for approval of drugs in foreign countries;
- reduced protection for intellectual property rights;
- the existence of additional third-party patent rights of potential relevance to our business;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with export control and import laws and regulations;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country;
- foreign reimbursement, pricing and insurance regimes;
- workforce uncertainty in countries where labor unrest is common;
- differing regulatory requirements with respect to manufacturing of products;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad;
- business interruptions resulting from geopolitical actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods and fires; and
- disruptions resulting from the impact of public health pandemics or epidemics (including, for example, the COVID-19 pandemic).

***Even if we obtain regulatory approval for Buntanetap or any product candidates, we will still face extensive and ongoing regulatory requirements and obligations and any product candidates, if approved, may face future development and regulatory difficulties.***

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, packaging, distribution, adverse event reporting, storage, recordkeeping, export, import, advertising and promotional activities for such product, among other things, will be subject to extensive and ongoing requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, establishment registration and drug listing requirements, continued compliance with cGMP requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping and GCP requirements for any clinical trials that we conduct post-approval.

Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product candidate may be marketed or to the conditions of approval, including a requirement to implement a REMS. If any of our product candidates receive marketing approval, the accompanying label may limit the approved indicated use of the product candidate, which could limit sales of the product candidate. The FDA may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of a product. The FDA closely regulates the post-approval marketing and promotion of drugs to ensure drugs are marketed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding off-label use, and if we market our products for uses beyond their approved indications, we may be subject to enforcement action for off-label marketing. Violations of the FDCA relating to the promotion of prescription drugs may lead to FDA enforcement actions and investigations alleging violations of federal and state healthcare fraud and abuse laws, as well as state consumer protection laws.

In addition, later discovery of previously unknown adverse events or other problems with our products, manufacturers or manufacturing processes or failure to comply with regulatory requirements, may yield various results, including:

- restrictions on manufacturing such products;
- restrictions on the labeling or marketing of products;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of our products;
- product seizure; or
- injunctions or the imposition of civil or criminal penalties.



Further, the FDA's policies may change, and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained, which would adversely affect our business, prospects and ability to achieve or sustain profitability.

We also cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. For example, certain policies of the current presidential administration may impact our business and industry. Namely, the current presidential administration has taken several executive actions, including the issuance of a number of Executive Orders, that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. It is difficult to predict how these executive actions will be implemented, and the extent to which they will impact the FDA's ability to exercise its regulatory authority. If these executive actions impose constraints on FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted.

***The FDA and other regulatory agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses.***

The FDA and other regulatory agencies strictly regulate the promotional claims that may be made about prescription products, such as Buntanetap or any future product candidates, if approved. In particular, a product may not be promoted for uses that are not approved by the FDA or such other regulatory agencies as reflected in the product's approved labeling. If we receive marketing approval for Buntanetap or any future product candidate, physicians may nevertheless prescribe it to their patients in a manner that is inconsistent with the approved label. If we are found to have promoted such off-label uses, we may become subject to significant liability. The U.S. federal government has levied large civil and criminal fines against companies for alleged improper promotion of off-label use and has enjoined several companies from engaging in off-label promotion. The government has also required companies to enter into consent decrees or imposed permanent injunctions under which specified promotional conduct is changed or curtailed. If we cannot successfully manage the promotion of Buntanetap or any future product candidates, if approved, we could become subject to significant liability, which would materially adversely affect our business and financial condition.

***We may seek a Breakthrough Therapy designation for Buntanetap from the FDA in PD and AD at the end of the first Phase 3 study in PD, and at the end of the Phase 2/3 study in AD, respectively. However, we might not receive such designation, and even if we do, such designation may not lead to a faster development or regulatory review or approval process.***

We may seek a Breakthrough Therapy designation for Buntanetap or one or more of our other product candidates. A Breakthrough Therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious 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. For drugs that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Drugs designated as breakthrough therapies by the FDA may also be eligible for priority review if supported by clinical data at the time the NDA is submitted to the FDA.

Designation as a Breakthrough Therapy is within the discretion of the FDA. Accordingly, even if we believe that one of our product candidates meets the criteria for designation as a Breakthrough Therapy, the FDA may disagree and instead determine not to make such designation. Even if we receive Breakthrough Therapy designation, the receipt of such designation for a product candidate may not result in a faster development or regulatory review or approval process compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that the product candidates no longer meet the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

***Potential product liability lawsuits against us could cause us to incur substantial liabilities and limit, delay or cease commercialization of any products that we may develop.***

The use of Buntanetap or any other product candidates we may develop in clinical trials and the sale of any products for which we obtain marketing approval exposes us to the risk of product liability claims. This risk will be even greater if we commercialize our product candidates, especially if our products are prescribed for off-label uses (even if we do not promote such uses). For example, we may be sued if our product candidates allegedly cause injury or are found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product candidate, negligence, strict liability and a breach of warranties. 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. Claims could also be asserted under state consumer protection acts. On occasion, large judgments have been awarded in class action lawsuits based on drugs that had unanticipated adverse effects. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs or be required to limit, delay or cease the commercialization of our products. Even a successful defense would require significant financial and management resources. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- impairment of our business reputation and significant negative media attention;
- withdrawal of participants from our clinical trials;
- significant costs to defend the litigation;
- distraction of management's attention and our resources from our primary business;
- substantial monetary awards to patients or other claimants;
- inability to commercialize Buntanetap or any other product candidate;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- decreased market demand for any product;
- significant negative financial impact; and
- a decline in our stock price.

The product liability insurance coverage we carry or acquire in the future may not be sufficient to reimburse us for any expenses or losses we may suffer. In connection with all our clinical studies, we carry insurance for product liability claims in the United States and in Europe. Insurance coverage is increasingly expensive. Our inability to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of Buntanetap or any future product candidates. Although we maintain such insurance, a successful product liability claim, or series of claims, brought against us could cause our share price to decline and, if judgments exceed our insurance coverage, could adversely affect the results of our operations and business, including preventing or limiting the commercialization of any product candidates we develop. Our insurance policies also have various exclusions, and we may be subject to a product liability claim for which we have no coverage.

***Our insurance policies are expensive and only protect us from some business risks, which will leave us exposed to significant uninsured liabilities.***

We do not carry insurance for all categories of risk that our business may encounter. Some of the policies we currently maintain include general liability, employment benefits liability, workers' compensation, products liability, and directors' and officers' insurance. We do not know, however, if we will be able to maintain insurance with adequate levels of coverage. No assurance can be given that an insurance carrier will not seek to cancel or deny coverage after a claim has occurred. Any significant

uninsured liability may require us to pay substantial amounts, which would adversely affect our financial position and results of operations.

## **Risks Related to Commercialization**

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

The biopharmaceutical and pharmaceutical industries are highly competitive and subject to significant and rapid technological change. Our success is highly dependent on our ability to acquire, develop, and obtain marketing approval for new products on a cost-effective basis and to market them successfully. If Buntanetap is approved, we will face intense competition from a variety of businesses, including large, fully integrated pharmaceutical companies, specialty pharmaceutical companies and biopharmaceutical companies in the United States and other jurisdictions. These organizations may have significantly greater resources than we do and may conduct similar research; seek patent protection; and establish collaborative arrangements for research, development, manufacturing and marketing of products that may compete with us.

Our competitors may, among other things:

- have significantly greater name recognition, financial, manufacturing, marketing, drug development, technical, and human resources than we do, and future mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors;
- develop and commercialize products that are safer, more effective, less expensive, more convenient, or easier to administer, or have fewer or less severe effects;
- obtain quicker regulatory approval;
- implement more effective approaches to sales and marketing; or
- form more advantageous strategic alliances.

Smaller and other early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel; establishing clinical trial sites and patient registration; and in acquiring technologies complementary to, or necessary for, our programs. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are more effective, have fewer or less severe side effects, or are more convenient or are less expensive than Buntanetap. Our competitors may also obtain FDA or other regulatory approval for their product candidates more rapidly than we may obtain approval for Buntanetap, which could result in our competitors establishing or strengthening their market position before we are able to enter the market. Competing products could present superior treatment alternatives, including by being more effective, safer, more convenient, less expensive or marketed and sold more effectively than any products we may develop. Competing products may render Buntanetap or any future product candidates we develop obsolete or noncompetitive before we recover the expense of developing and commercializing our product candidates. If we are unable to compete effectively, our opportunity to generate revenue from the sale of our products we may develop, if approved, could be adversely affected.

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

The availability and adequacy of coverage and reimbursement by governmental healthcare programs such as Medicare and Medicaid, private health insurers and other third-party payors are essential for most patients to be able to afford prescription medications such as Buntanetap, if approved. Our ability to achieve acceptable levels of coverage and reimbursement for products by governmental authorities, private health insurers and other organizations will have an effect on our ability to successfully commercialize our drug and any other product candidates we develop. Accordingly, we will need to successfully implement a

coverage and reimbursement strategy for any approved product candidate. Assuming we obtain coverage for our product candidates by a third-party payor, the resulting reimbursement payment rates may not be adequate or may require co-payments that patients find unacceptably high. We cannot be sure that coverage and reimbursement in the United States or elsewhere will be available for our product candidates or any product that we may develop, and any reimbursement that may become available may be decreased or eliminated in the future.

For products administered under the supervision of a physician, obtaining coverage and adequate reimbursement may be particularly difficult because of the higher prices often associated with such drugs. Additionally, separate reimbursement for the product itself or the treatment or procedure in which the product is used may not be available, which may impact physician utilization. We cannot be sure that coverage and reimbursement in the United States, the European Union or elsewhere will be available, or at an acceptable level, for any product that we may develop, and any reimbursement that may become available may be decreased or eliminated in the future.

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

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

No uniform policy for coverage and reimbursement for products exists among third-party payors in the United States. Therefore, coverage and reimbursement for products can differ significantly from payor to payor. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our product candidates to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance. Furthermore, rules and regulations regarding reimbursement change frequently, in some cases at short notice, and we believe that changes in these rules and regulations are likely.

We may also be subject to extensive governmental price controls and other market regulations outside of the United States, and we believe the increasing emphasis on cost-containment initiatives in other countries have and will continue to put pressure on the pricing and usage of medical products. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. Other countries allow companies to fix their own prices for medical products 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 product candidates may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenue and profits.

Moreover, increasing efforts by governmental and third-party payors in the United States to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for newly approved products and, as a result, they may not cover or provide adequate payment for our product candidates. We expect to experience pricing pressures in connection with the sale of our product candidates due to the trend toward managed health care, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs

and biologics and surgical procedures and other treatments, has become intense. As a result, increasingly high barriers are being erected to the entry of new products.

***Even if Buntanetap or any product candidate we develop receives marketing approval, it may fail to achieve market acceptance by physicians, patients, third-party payors or others in the medical community necessary for commercial success, which would adversely affect our business.***

Buntanetap and any future product candidates may not be commercially successful. If Buntanetap or any other product candidate we develop receives marketing approval, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. If it does not achieve an adequate level of acceptance, we may not generate significant product revenues or become profitable. The degree of market acceptance of our product candidates, if approved, will depend on a number of factors, including but not limited to:

- the efficacy and potential advantages compared to alternative treatments;
- the indications for which our product candidates are approved;
- the limitation of our targeted patient population and other limitations or warnings contained in any FDA-approved labeling;
- effectiveness of sales and marketing efforts;
- the cost of treatment in relation to alternative treatments, including any similar generic treatments;
- our ability to offer our products for sale at competitive prices;
- the convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support;
- the availability of third-party coverage and adequate reimbursement;
- the willingness of patients to pay all, or a portion of, out-of-pocket costs associated with our products in the absence of sufficient third-party coverage and adequate reimbursement;
- the prevalence and severity of any side effects;
- any restrictions on the use of our product together with other medications;
- potential product liability claims;
- the timing of market introduction of our products as well as availability, safety and efficacy of competitive drugs; and
- unfavorable publicity relating to the product.

Because we expect sales of our product candidates, if approved, to generate substantially all of our revenues for the foreseeable future, the failure of our product candidates to find market acceptance would harm our business and could require us to seek additional financing. Our efforts to educate the medical community and third-party payors regarding the benefits of our products may require significant resources and may never be successful.

***If we are unable to establish sales, marketing and distribution capabilities, we may not be successful in commercializing Buntanetap, if approved.***

We do not have any infrastructure for the sales, marketing or distribution of Buntanetap, and the cost of establishing and maintaining such an organization may exceed the cost-effectiveness of doing so. In order to market and successfully commercialize our drug or any product candidate we develop, if approved, we must build our sales, distribution, marketing, managerial and other non-technical capabilities or collaborate with third parties to perform these services.

We do not anticipate having the resources in the foreseeable future to allocate to the sales and marketing of our product candidates, if approved, in certain markets overseas. Therefore, our future success will depend, in part, on our ability to enter into and maintain collaborative relationships for such capabilities, the collaborator's strategic interest in a product and such collaborator's ability to successfully market and sell the product. We intend to pursue collaborative arrangements regarding the sale and marketing of Buntanetap, if approved, for certain markets overseas; however, there can be no assurance that we will be able to establish or maintain such collaborative arrangements, or if able to do so, that they will have effective sales forces. To the extent that we depend on third parties for marketing and distribution, any revenues we receive will depend upon the efforts of such third parties, and there can be no assurance that such efforts will be successful.

If we are unable to build our own sales force or negotiate a collaborative relationship for the commercialization of Buntanetap, we may be forced to delay the potential commercialization of the drug or reduce the scope of our sales or marketing activities. If we need to increase our expenditures to fund commercialization activities for Buntanetap we will need to obtain additional capital, which may not be available to us on acceptable terms, or at all. We may also have to enter into collaborative arrangements for Buntanetap at an earlier stage than otherwise would be ideal and we may be required to relinquish rights to it or otherwise agree to terms unfavorable to us. Any of these occurrences may have an adverse effect on our business, operating results and prospects.

If we are unable to establish adequate sales, marketing and distribution capabilities, we will not be successful in commercializing our product candidates and may never become profitable. We will be competing with many companies that currently have extensive and well-funded marketing and sales operations. Without an internal team or the support of a third party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

***A variety of risks associated with operating internationally could materially adversely affect our business.***

We currently have no international operations, but our business strategy includes potentially expanding internationally if any of our product candidates receive regulatory approval. Doing business internationally involves a number of risks, including but not limited to:

- the burden of complying with multiple, conflicting and changing laws and regulations, such as privacy regulations, tax laws, export and import restrictions, employment laws, regulatory requirements and other governmental approvals, permits and licenses;
- failure by us to obtain and maintain regulatory approvals for the use of our products in various jurisdictions;
- additional potentially relevant third-party patent rights;
- complexities and difficulties in obtaining protection and enforcing our intellectual property;
- difficulties in staffing and managing foreign operations;
- complexities associated with managing multiple payor reimbursement regimes, government payors or patient self-pay systems;
- limits in our ability to penetrate international markets;

- financial risks, such as longer payment cycles, difficulty collecting accounts receivable, the impact of local and regional financial crises on demand and payment for our products and exposure to foreign currency exchange rate fluctuations;
- natural disasters, political and economic instability, including wars, terrorism and political unrest, outbreak of disease, boycotts, curtailment of trade and other business restrictions;
- certain expenses including, among others, expenses for travel, translation and insurance; and
- regulatory and compliance risks that relate to maintaining accurate information and control over sales and activities that may fall within the purview of the U.S. Foreign Corrupt Practices Act, its books and records provisions, or its anti-bribery provisions.

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

### **Risks Related to Our Dependence on Third Parties**

***Our employees and independent contractors, including principal investigators, CROs, consultants, vendors, and any third parties we may engage in connection with development and commercialization, may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could have a material adverse effect on our business.***

Our employees and independent contractors, including principal investigators, consultants, vendors and any third parties we may engage in connection with development and commercialization of our product candidates, could engage in misconduct, including intentional, reckless or negligent conduct or unauthorized activities that violate: the laws and regulations of the FDA or other similar regulatory requirements of other authorities, including those laws that require the reporting of true, complete and accurate information to such authorities; manufacturing standards; data privacy, security, fraud and abuse and other healthcare laws and regulations; or laws that require the reporting of true, complete and accurate financial information and data. Specifically, 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. Activities subject to these laws could also involve the improper use or misrepresentation of information obtained in the course of clinical trials, creation of fraudulent data in preclinical studies or clinical trials or illegal misappropriation of drug product, which could result in regulatory sanctions and cause serious harm to our reputation. It is not always possible to identify and deter misconduct by employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with such laws or regulations. Additionally, we are subject to the risk that a person or government could allege such fraud or other misconduct, even if none occurred. If any such actions are instituted against us and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant civil, criminal and administrative penalties, damages, monetary fines, disgorgements, possible exclusion from participation in Medicare, Medicaid, other U.S. federal healthcare programs or healthcare programs in other jurisdictions, individual imprisonment, other sanctions, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations.

***We currently rely on a third-party contract manufacturing organization (“CMO”), for the production of clinical supply of Buntanetap and intend to rely on CMOs for the production of commercial supply of Buntanetap, if approved. Our dependence on CMOs may impair the development and commercialization of the drug, which would adversely impact our business and financial position.***

We have limited personnel with experience in manufacturing, and we do not own facilities for manufacturing. Instead, we rely on and expect to continue to rely on CMOs for the supply of cGMP grade clinical trial materials and commercial quantities of Buntanetap and any product candidates we develop, if approved. Reliance on CMOs may expose us to more risk than if we were to manufacture our product candidates ourselves. We intend to have manufactured a sufficient clinical supply of Buntanetap drug substance to enable us to complete our clinical trials, and we have also engaged two CMOs to provide clinical and commercial supply of the drug product.

The facilities used to manufacture our product candidates must be inspected by the FDA and comparable foreign authorities. While we provide oversight of manufacturing activities, we do not and will not control the execution of manufacturing activities by, and are or will be essentially dependent on, our CMOs for compliance with cGMP requirements for the manufacture of our product candidates. As a result, we are subject to the risk that our product candidates may have manufacturing defects that we have limited ability to prevent. If a CMO cannot successfully manufacture material that conforms to our specifications and the regulatory requirements, we will not be able to secure or maintain regulatory approval for the use of our product candidates in clinical trials, or for commercial distribution of our product candidates, if approved. In addition, we have limited control over the ability of our CMOs to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or comparable foreign regulatory authority finds deficiencies with or does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval or finds deficiencies in the future, we may need to find alternative manufacturing facilities, which would delay our development program and significantly impact our ability to develop, obtain regulatory approval for or commercialize our product candidates, if approved. In addition, any failure to achieve and maintain compliance with these laws, regulations and standards could subject us to the risk that we may have to suspend the manufacture of our product candidates or that obtained approvals could be revoked. Furthermore, CMOs may breach existing agreements they have with us because of factors beyond our control. They may also terminate or refuse to renew their agreement at a time that is costly or otherwise inconvenient for us. If we were unable to find an adequate CMO or another acceptable solution in time, our clinical trials could be delayed, or our commercial activities could be harmed.

We rely on and will continue to rely on CMOs to purchase from third-party suppliers the raw materials necessary to produce our product candidates. We do not and will not have control over the process or timing of the acquisition of these raw materials by our CMOs. Supplies of raw material could be interrupted from time to time and we cannot be certain that alternative supplies could be obtained within a reasonable timeframe, at an acceptable cost, or at all. In addition, a disruption in the supply of raw materials could delay the commercial launch of our product candidates, if approved, or result in a shortage in supply, which would impair our ability to generate revenues from the sale of our product candidates. Growth in the costs and expenses of raw materials may also impair our ability to cost effectively manufacture our product candidates. There are a limited number of suppliers for the raw materials that we may use to manufacture our product candidates and we may need to assess alternative suppliers to prevent a possible disruption of the manufacture of our product candidates.

Finding new CMOs or third-party suppliers involves additional cost and requires our management's time and focus. In addition, there is typically a transition period when a new CMO commences work. Although we generally have not, and do not intend to, begin a clinical trial unless we believe we have on hand, or will be able to obtain, a sufficient supply of our product candidates to complete the clinical trial, any significant delay in the supply of our product candidates or the raw materials needed to produce our product candidates, could considerably delay conducting our clinical trials and potential regulatory approval of our product candidates.

As part of their manufacture of our product candidates, our CMOs and third-party suppliers are expected to comply with and respect the proprietary rights of others. If a CMO or third-party supplier fails to acquire the proper licenses or otherwise infringes the proprietary rights of others in the course of providing services to us, we may have to find alternative CMOs or third-party suppliers or defend against claims of infringement, either of which would significantly impact our ability to develop, obtain regulatory approval for or commercialize our product candidates, if approved.

***We currently rely and in the future intend to rely on third parties to conduct, supervise and monitor our clinical trials. If those third parties do not successfully carry out their contractual duties, or if they perform in an unsatisfactory manner, it may harm our business.***

We rely, and will continue to rely, on CROs, CRO-contracted vendors and clinical trial sites to ensure the proper and timely conduct of our clinical trials. Our reliance on CROs for clinical development activities limits our control over these activities, yet we remain responsible for ensuring that each of our trials is conducted in accordance with the applicable protocol and legal, regulatory and scientific standards.

We and our CROs will be required to comply with the Good Laboratory Practice requirements for our preclinical studies and GCP requirements for our clinical trials, which are regulations and guidelines enforced by the FDA and are also required by comparable foreign regulatory authorities. Regulatory authorities enforce GCP requirements through periodic inspections of trial sponsors, principal investigators and clinical trial sites. If we or our CROs fail to comply with GCP requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to



perform additional clinical trials before approving our marketing applications. There can be no assurance that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP requirements. In addition, our clinical trials must be conducted with product produced under cGMP requirements. Accordingly, if our CROs fail to comply with these requirements, we may be required to repeat clinical trials, which would delay the regulatory approval process.

Our CROs are not our employees, and we do not control whether or not they devote sufficient time and resources to our clinical trials. Our CROs 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, which could harm our competitive position. We face the risk of potential unauthorized disclosure or misappropriation of our intellectual property by CROs, which may reduce our trade secret protection and allow our potential competitors to access and exploit our proprietary technology. If our 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 reason, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for, or successfully commercialize any product candidate that we develop. As a result, our financial results and the commercial prospects for any product candidate that we develop would be harmed, our costs could increase, and our ability to generate revenue could be delayed.

If our relationship with any CROs terminate, we may not be able to enter into arrangements with alternative CROs or do so on commercially reasonable terms. Switching or adding additional CROs involves substantial cost and requires management's time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays occur, which can materially impact our ability to meet our desired clinical development timelines. Though we intend to carefully manage our relationships with our CROs, there can be no assurance that we will not encounter challenges or delays in the future or that these delays or challenges will not have an adverse impact on our business, financial condition and prospects.

- the number and type of our collaborations could adversely affect our attractiveness to future collaborators or acquirers; and
- the loss of, or a disruption in our relationship with, any one or more collaborators could harm our business.

If any collaborations do not result in the successful development and commercialization of products or if one of our collaborators terminates its agreement with us, we may not receive any future research and development funding or milestone or royalty payments under such collaborations. If we do not receive the funding we expect under these agreements, our continued development of our product candidates could be delayed, and we may need additional resources to develop additional product candidates. All of the risks relating to product development, regulatory approval and commercialization described in this Annual Report on Form 10-K also apply to the activities of any collaborators and there can be no assurance that our collaborations will produce positive results or successful products on a timely basis or at all.

In addition, subject to its contractual obligations to us, if one of our collaborators is involved in a business combination or otherwise changes its business priorities, the collaborator might deemphasize or terminate the development or commercialization of our product candidates. If a collaborator terminates its agreement with us, we may find it more difficult to attract new collaborators and the perception of our business and our stock price could be adversely affected.

We may in the future collaborate with additional pharmaceutical and biotechnology companies for development and potential commercialization of therapeutic products. We face significant competition in seeking appropriate collaborators. Our ability to reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms, or at all, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market or continue to develop our programs, and our business may be materially and adversely affected.

## Risks Related to Healthcare Laws and Other Legal Compliance Matters

***Enacted and future healthcare legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates, if approved, and may affect the prices we may set.***

In the United States and other jurisdictions, there have been, and we expect there will continue to be, a number of legislative and regulatory changes and proposed changes to the healthcare system that could affect our future results of operations. In particular, there have been and continue to be a number of initiatives at the U.S. federal and state levels that seek to reduce healthcare costs and improve the quality of healthcare. For example, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act (collectively the “ACA”) was enacted, which substantially changed the way healthcare is financed by both governmental and private insurers.

Since its enactment, there have been judicial and Congressional challenges to certain aspects of the ACA, and we expect there may be additional challenges and amendments to the ACA in the future. It is uncertain the extent to which any such changes may impact our business or financial condition.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. For example, the Budget Control Act of 2011, resulted in aggregate reductions of Medicare payments to providers of 2% per fiscal year. These reductions went into effect in April 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2027 unless additional action is taken by Congress. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Additionally, the orphan drug tax credit was reduced as part of a broader tax reform. These new laws or any other similar laws introduced in the future may result in additional reductions in Medicare and other health care funding, which could negatively affect our customers and accordingly, our financial operations.

In addition, there has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been Congressional inquiries and proposed federal and state legislation designed to bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs and reform government program reimbursement methodologies for drugs. Moreover, payment methodologies may be subject to changes in healthcare legislation and regulatory initiatives. We expect that additional U.S. federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that the U.S. federal government will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

Individual states in the United States have also become increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. Legally mandated price controls on payment amounts by third-party payors or other restrictions could harm our business, results of operations, financial condition and prospects. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. This could reduce the ultimate demand for our product candidates or put pressure on our product pricing.

In markets outside of the United States, reimbursement and healthcare payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. We cannot predict the likelihood, nature, or extent of government regulation that may arise from future legislation or administrative action in the United States or any other jurisdiction. If we or any third parties we may engage are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we or such third parties are not able to maintain regulatory compliance, our product candidates may lose any regulatory approval that may have been obtained and we may not achieve or sustain profitability.

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

Our business operations and current and future arrangements with investigators, healthcare professionals, consultants, third-party payors, patient organizations, and customers, may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations. These laws may constrain the business or financial arrangements and relationships through which we conduct our operations, including how we research, market, sell and distribute our product candidates, if approved. Such laws include:

- the U.S. federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, offering, receiving, or providing any remuneration (including any kickback, bribe, or certain rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, lease, order, or recommendation of, any good, facility, item, or service, for which payment may be made, in whole or in part, under U.S. federal and state healthcare programs such as Medicare and Medicaid. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. The U.S. federal Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers on the other hand;
- the U.S. federal false claims and civil monetary penalties laws, including the civil False Claims Act (“FCA”) which, among other things, impose criminal and civil penalties, including through civil whistleblower or *qui tam* actions, against individuals or entities for knowingly presenting, or causing to be presented, to the U.S. federal government, claims for payment or approval that are false or fraudulent, knowingly making, using or causing to be made or used, a false record or statement material to a false or fraudulent claim, or from knowingly making a false statement to avoid, decrease or conceal an obligation to pay money to the U.S. federal government. In addition, the government may assert that a claim including items and services resulting from a violation of the U.S. federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the FCA. A claim includes “any request or demand” for money or property presented to the federal government. In addition, manufacturers can be held liable under the FCA even when they do not submit claims directly to government payors if they are deemed to “cause” the submission of false or fraudulent claims;
- Health Insurance Portability and Accountability Act of 1996 (“HIPAA”), which imposes criminal and civil liability for, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement, in connection with the delivery of, or payment for, healthcare benefits, items or services. Similar to the U.S. federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 (“HITECH”) and their respective implementing regulations, which impose, among other things, specified requirements relating to the privacy, security and transmission of individually identifiable health information without appropriate authorization by covered entities subject to the rule, such as health plans, healthcare clearinghouses and healthcare providers as well as their business associates that perform certain services involving the use or disclosure of individually identifiable health information. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys’ fees and costs associated with pursuing federal civil actions;
- the Federal Food, Drug and Cosmetic Act (“FDCA”), which prohibits, among other things, the adulteration or misbranding of drugs, biologics and medical devices;
- the U.S. federal legislation commonly referred to as the Physician Payments Sunshine Act, enacted as part of the ACA, and its implementing regulations, which requires certain manufacturers of drugs, devices, biologics, and medical supplies

that are reimbursable under Medicare, Medicaid, or the Children's Health Insurance Program to report annually to the government information related to certain payments and other transfers of value to physicians and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members; and

- analogous U.S. state laws and regulations, including: state anti-kickback and false claims laws, which may apply to our business practices, including but not limited to, research, distribution, sales, and marketing arrangements and claims involving healthcare items or services reimbursed by any third-party payor, including private insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the U.S. federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws and regulations that require drug manufacturers to file reports relating to pricing and marketing information, which requires tracking gifts and other remuneration and items of value provided to healthcare professionals and entities; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Because of the breadth of these laws and the narrowness of the statutory exceptions and regulatory safe harbors available under such laws, it is possible that some of our business activities, including our consulting agreements and other relationships with physicians and other healthcare providers, some of whom receive stock or stock options as compensation for their services, could be subject to challenge under one or more of such laws. Ensuring that our current and future internal operations and business arrangements with third parties comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations, agency guidance or case law involving applicable fraud and abuse or other healthcare laws and regulations.

If our operations are found to be in violation of any of the laws described above or any other governmental laws and regulations that may apply to us, we may be subject to the imposition of civil, criminal and administrative penalties, damages, disgorgement, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, individual imprisonment, contractual damages, reputational harm, diminished profits and future earnings, additional reporting requirements or oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, and curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. If any of the physicians or other providers or entities with whom we expect to do business are found to not be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs and imprisonment, which could affect our ability to operate our business. Further, defending against any such actions can be costly, time-consuming and may require significant personnel resources. Therefore, even if we are successful in defending against any such actions that may be brought against us, our business may be impaired.

***Any clinical trial programs we conduct or research collaborations we enter into in the EEA may subject us to the General Data Protection Regulation.***

If we conduct clinical trial programs or enter into research collaborations in the EEA, we may be subject to the General Data Protection regulation ("GDPR"). The GDPR applies extraterritorially and implements stringent operational requirements for processors and controllers of personal data, including, for example, high standards for obtaining consent from individuals to process their personal data, robust disclosures to individuals, a comprehensive individual data rights regime, data export restrictions governing transfers of data from the European Union ("EU") to other jurisdictions, short timelines for data breach notifications, limitations on retention of information, increased requirements pertaining to health data, other special categories of personal data and coded data and additional obligations if we contract third-party processors in connection with the processing of personal data. The GDPR provides that EU member states may establish their own laws and regulations limiting the processing of personal data, including genetic, biometric or health data, which could limit our ability to use and share personal data or could cause our costs to increase. If our or our partners' or service providers' privacy or data security measures fail to comply with the GDPR requirements, we may be subject to litigation, regulatory investigations, enforcement notices requiring us to change the way we use personal data and/or fines of up to €20 million or up to 4% of the total worldwide annual turnover of the preceding financial year, whichever is higher, as well as compensation claims by affected individuals, negative publicity, reputational harm and a potential loss of business and goodwill.

***We are subject to U.S. and certain foreign export and import controls, sanctions, embargoes, anti-corruption laws and anti-money laundering laws and regulations. Compliance with these legal standards could impair our ability to compete in domestic and international markets. We could face criminal liability and other serious consequences for violations, which could harm our business.***

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

Furthermore, U.S. export control laws and economic sanctions prohibit the provision of certain products and services to countries, governments, and persons targeted by U.S. sanctions. U.S. sanctions that have been or may be imposed as a result of military conflicts in other countries may impact our ability to continue activities at future clinical trial sites within regions covered by such sanctions. If we fail to comply with export and import regulations and such economic sanctions, penalties could be imposed, including fines and/or denial of certain export privileges. These export and import controls and economic sanctions could also adversely affect our supply chain.

***We are subject to environmental, health and safety laws and regulations, and we may become exposed to liability and substantial expenses in connection with environmental compliance or remediation activities.***

We and any contract manufacturers and suppliers we engage are subject to numerous environmental, health and safety laws and regulations. These laws and regulations govern, among other things, the controlled use, handling, release and disposal of and the maintenance of a registry for, hazardous materials and biological materials, such as chemical solvents, human cells, carcinogenic compounds, mutagenic compounds and compounds that have a toxic effect on reproduction, laboratory procedures and exposure to blood-borne pathogens. While the materials we use require operations involving the use of hazardous and flammable materials, including chemicals and biological materials, we do not produce any materials ourselves and contract with third parties for the manufacture and the disposal of these materials and wastes.

As with other companies engaged in activities similar to ours, we face a risk of environmental liability inherent in our current and historical activities, including liability relating to releases of or exposure to hazardous or biological materials. Environmental, health and safety laws and regulations are becoming more stringent. We may be required to incur substantial expenses in connection with future environmental compliance or remediation activities, in which case, the production efforts of our third-party manufacturers or our development efforts may be interrupted or delayed.

***Recent U.S. tax legislation may materially adversely affect our financial condition, results of operations and cash flows.***

On March 27, 2020, the Coronavirus Aid, Relief, and Economic Security Act ("CARES Act") was enacted in response to the COVID-19 pandemic. The CARES Act, among other things, permits NOL carryovers and carrybacks to offset 100% of taxable income for taxable years beginning before 2021. Previously, NOLs generated after December 31, 2017 were limited to 80% of taxable income in future years. In addition, the CARES Act allows NOLs incurred in 2018, 2019 and 2020 to be carried back to each of the five preceding taxable years to generate a refund of previously paid income taxes. The NOL carryback provision of the CARES Act had no impact on us due to our tax losses generated during all prior years.

U.S. tax legislation enacted in 2017 has significantly changed the U.S. federal income taxation of U.S. corporations, including by reducing the U.S. corporate income tax rate, limiting interest deductions, and revising the rules governing NOLs. The legislation could be subject to potential amendments and technical corrections, as well as interpretations and implementing regulations by the U.S. Treasury and Internal Revenue Service, any of which could lessen or increase certain adverse impacts of the legislation. In addition, it is unclear how these U.S. federal income tax changes will affect state and local taxation, which often uses federal taxable income as a starting point for computing state and local tax liabilities.

## **Risks Related to Our Intellectual Property**

***If we are unable to obtain, maintain and enforce patent or other intellectual property protection for Buntanetap or any future product candidates or technology or if the scope of the patent protection obtained is not sufficiently broad, our competitors or other third parties could develop and commercialize products similar or identical to ours, our ability to successfully commercialize Buntanetap or any future product candidates may be adversely affected and 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 drug development programs and product candidates. These legal measures afford only limited protection, and competitors or others may gain access to or use our intellectual property and proprietary information. Our success depends in large part on our ability to obtain, maintain and defend patent protection in the United States and other countries with respect to Buntanetap and any future product candidates. Because we have not conducted a formal freedom to operate analysis for patents related to Buntanetap since 2008, we may not be aware of patents issued since then that a third-party might assert are infringed by Buntanetap or any future product candidates, which could materially impair our ability to commercialize Buntanetap or any future product candidates. We generally seek to protect our proprietary position, in part, by filing patent applications in the United States and abroad relating to Buntanetap and any future product candidates, manufacturing processes, and methods of use. If we are unable to obtain, maintain or enforce patent protection, our business, financial condition, results of operations and prospects could be materially harmed.

Changes in either the patent laws or their interpretation in the United States and other jurisdictions may diminish our ability to protect our intellectual property, obtain, maintain and enforce our intellectual property rights and, more generally, could affect the value of our intellectual property or narrow the scope of our protection. We cannot predict whether the patent applications we currently or may in the future pursue will issue as patents in any particular jurisdiction, will provide sufficient protection against competitors or other third parties, or if these patents are challenged by our competitors, will be found to be invalid, unenforceable, or not infringed. Our pending and future patent applications may not result in patents being issued which protect our technology or product candidates, in whole or in part, or which effectively prevent others from commercializing competitive technologies and product candidates. It is also possible that we will fail to identify patentable aspects of our research and development output in time to obtain patent protection before public disclosures are made. Although we enter into non-disclosure and confidentiality agreements with parties who have access to confidential or patentable aspects of our research and development output, such as our employees, third-party collaborators, CROs, contract manufacturers, consultants, advisors and other third parties, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. Consequently, we may not be able to prevent any third party from using any of our technology that is in the public domain to compete with Buntanetap and any future product candidates or technologies. In addition, our ability to obtain and maintain valid and enforceable patents depends on whether the differences between our inventions and the prior art allow our inventions to be patentable in light of the prior art. Furthermore, publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we or our licensors were the first to invent the inventions claimed in any of our licensed patents or pending patent applications, or that we or our licensors were the first to make the inventions claimed in those owned or licensed patents or pending patent applications, or that we or our licensors were the first to file for patent protection of such inventions. If a third party can establish that we or our licensors were not the first to make or the first to file for patent protection of such inventions, our owned or licensed patents and patent applications may not issue as patents and even if issued, may be challenged and invalidated or rendered unenforceable. Furthermore, even if a patent is granted, our competitors or other third parties may be able to circumvent the patent by developing similar or alternative technologies or products in a non-infringing manner which could materially adversely affect our business, financial condition, results of operations and prospects.

***If we are unable to obtain additional patent protection to prolong the patent life of our product candidates, we may not be able to continue development of our product candidate.***

We seek to protect and prolong our proprietary position by filing patent applications in the United States and abroad related to our development programs and product candidates. If the patent applications we own with respect to our development programs and product candidates fail to issue, if their breadth or strength of protection is threatened, or if they fail to provide meaningful exclusivity for Buntanetap or any future product candidate, it could dissuade companies from collaborating with us to develop product candidates, and threaten our ability to commercialize future product candidates. Any such outcome could have a materially adverse effect on our business and our company could cease to exist.

Annovis has filed seven families of patent applications to prolong the patent life of Buntanetap. Unless these applications are approved by the U.S. and international patent offices, the patent life of using Buntanetap is limited. The first patent application family we filed, which would be expected to expire in 2031, covers the use of Buntanetap at much lower doses and expands its use to the treatment of AD, PD and other neurodegenerative disorders such as Huntington's disease, prion diseases, amyotrophic lateral sclerosis, tauopathies and frontotemporal dementia, based on our preclinical research. In August 2019, the USPTO granted the first of our Annovis patents from this family covering PD and Lewy body diseases. Subsequently the USPTO also granted patents covering tau and tauopathies, chronic traumatic encephalopathy, prion diseases, amyotrophic lateral sclerosis, Alzheimer's and Huntington's disease. The second patent application family covers ANVS405's use in acute brain and nerve trauma and would be expected to expire in 2036, before any patent term adjustments or extensions. In December 2020, the EPO approved the whole patent, and it has since been approved in number of other countries. However, the USPTO entered a species restriction as to the condition being treated and we are therefore currently pursuing claims directed to traumatic brain injury. We intend to file additional divisional applications when we have successfully reached a conclusion to the pending application, assuming we are not able to cover the remaining acute conditions (stroke, nerve injury and spinal cord injury) for which patent coverage is being sought in the pending application. The third patent application family relates to the use of the mechanism of action of Buntanetap and ANVS405 to prevent and treat neurodegenerative diseases and would be expected to expire in 2038, before any patent term adjustments or extensions. The first divisional of this application was approved in December 2022; it covers the prevention of neurodegenerative diseases and we are awaiting the official publishing of the patent. In May 2020, we filed a patent application with the USPTO concerning a method of inhibiting, preventing, or treating neurological injuries due to viral, bacterial, fungal, protozoan, or parasitic infections in humans and in animals via administration of Buntanetap or related compounds which would be expected to expire in 2041, before any patent term adjustments or extensions; we have not received any office actions, yet. Recently we also filed three provisional patents - Buntanetap in cancer, Buntanetap and combinations, Buntanetap in neuropsychiatric indications. While the issuance of our new patents gives us some comfort that the patent life relating to methods of using Buntanetap may be prolonged to 2031, 2036 and 2038, the fact that only a portion of the family claims has so far been allowed could result in very limited patent coverage. It is possible that we will fail to identify further patentable aspects of our research and development output before it is too late to obtain patent protection. The patent applications that we own may fail to result in issued patents with claims that provide further coverage of Buntanetap or any other product candidate in the United States or in other foreign countries.

***Our patents may be challenged in courts, in patent offices or before other administrative bodies which could result in the invalidation, narrowing or unenforceability of our patents and our patent portfolio, along with the unpredictable nature of patent prosecution, may not provide us with sufficient rights to similarly challenge other parties or exclude others from commercializing products similar or identical to ours.***

Even if patents do successfully issue and even if such patents further cover Buntanetap or any future product candidate, third parties may challenge their validity, enforceability or scope, which may result in such patents being narrowed, invalidated, or held unenforceable. Our patent rights may be subject to such priority, validity, inventorship, scope and enforceability disputes. Legal proceedings relating to intellectual property claims, with or without merit, are unpredictable and generally expensive and time-consuming and likely to divert significant resources from our core business, including distracting our management and scientific personnel from their normal responsibilities and generally harm our business. 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. If we encounter delays in regulatory approvals, the period during which we could market a product candidate under patent protection could be reduced.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. In addition, the laws of foreign countries may not

protect our rights to the same extent as the laws of the United States. For example, European patent law restricts the patentability of methods of treatment of the human body more than U.S. law does. However, in certain instances, the laws of the United States are more restrictive than those of foreign countries. For example, a recent series of U.S. Supreme Court cases has narrowed the types of subject matter considered eligible for patenting. Accordingly, certain diagnostic methods are considered ineligible for patenting because they are directed to a “law of nature.” Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in patent claims being narrowed, invalidated, held unenforceable, in whole or in part, or reduced in term. Such a result could limit our ability to stop others from using or commercializing similar or identical technology and products.

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

We or our licensors may be subject to claims that former employees, consultants, collaborators or other third parties have an interest in our patent rights, any potential trade secrets, or other intellectual property as an inventor, co-inventor or owner of any potential trade secrets. For example, we may have inventorship disputes arise from conflicting obligations of consultants or others who are involved in developing our product candidates and other proprietary technologies we may develop. Litigation may be necessary to defend against these and other claims challenging inventorship or our patent rights, any potential trade secrets or other intellectual property. If we or our licensors 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, intellectual property that is important to our product candidates and other proprietary technologies we may develop. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to our management and other employees. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

***We may become subject to third parties’ claims alleging infringement of their patents and proprietary rights, or we may need to become involved in lawsuits to protect or enforce our patents, which could be costly, time consuming, delay or prevent the development and commercialization of our product candidates or put our patents and other proprietary rights at risk.***

Our commercial success depends, in part, upon our ability to develop, manufacture, market and sell our product candidates without alleged or actual infringement, misappropriation or other violation of the patents and proprietary rights of third parties. Litigation relating to infringement or misappropriation of patent and other intellectual property rights in the pharmaceutical and biotechnology industries is common, including patent infringement lawsuits, interferences, oppositions and reexamination proceedings before the USPTO and corresponding foreign patent offices. The various markets in which we plan to operate are subject to frequent and extensive litigation regarding patents and other intellectual property rights. In addition, many companies in intellectual property-dependent industries, including the biotechnology and pharmaceutical industries, have employed intellectual property litigation as a means to gain an advantage over their competitors. Numerous U.S., EU and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are developing product candidates. Some claimants may have substantially greater resources than we do and may be able to sustain the costs of complex intellectual property litigation to a greater degree and for longer periods of time than we could. In addition, patent holding companies that focus solely on extracting royalties and settlements by enforcing patent rights may target us. 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 intellectual property rights of third parties.

We may be subject to third-party claims including infringement, interference or derivation proceedings, post-grant review and *inter partes* review before the USPTO or similar adversarial proceedings or litigation in other jurisdictions. Even if we believe third party infringement claims are without merit, a court of competent jurisdiction could hold that these third-party patents are valid, enforceable and infringed, and the holders of any such patents may be able to block our ability to commercialize the applicable product candidate unless we obtained a license under the applicable patents, or until such patents expire or are finally determined to be invalid or unenforceable. Proceedings challenging our patents or those that we license may also result in our patent claims being invalidated or narrowed in scope. Similarly, if our patents or patent applications are challenged during interference or derivation proceedings, a court may hold that a third-party is entitled to certain patent ownership rights instead of us. Further, if any third-party patents were held by a court of competent jurisdiction to cover aspects of our compositions, formulations, methods of manufacture, or methods of treatment, prevention or use, the holders of any such patents may be able to block our ability to develop and commercialize the applicable product candidate unless we obtained a license or until such patent expires or is finally determined to be



invalid or unenforceable. In addition, defending such claims would cause us to incur substantial expenses and, if successful, could cause us to pay substantial damages, if we are found to be infringing a third party's patent rights. If we are found to have infringed such rights willfully, the damages may be enhanced and may include attorneys' fees. Further, if a patent infringement suit is brought against us or our third-party service providers, our development, manufacturing or sales activities relating to the product or product candidate that is the subject of the suit may be delayed or terminated. Modifying our product candidates to design around third-party intellectual property rights may result in significant cost or delay to us and could prove to be technically infeasible. Any of these events, even if we were ultimately to prevail, could require us to divert substantial financial and management resources that we would otherwise be able to devote to our business. In addition, if the breadth or strength of protection provided the patents and patent applications we own or in-license is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

If we were to initiate legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that our patent is invalid or unenforceable. In patent litigation in the United States and in Europe, 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, for example, lack of eligibility, lack of novelty, obviousness or non-enablement. Third parties might allege unenforceability of our patents because someone connected with prosecution of the patent withheld relevant information, or made a misleading statement, during prosecution. The outcome of proceedings involving assertions of invalidity and unenforceability during patent litigation is unpredictable. With respect to the validity of patents, 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. Furthermore, our patents and other intellectual property rights also will not protect our technology if competitors design around our protected technology without infringing on our patents or other 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 view these announcements in a negative light, the price of our common stock could be adversely affected.

Finally, even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors view these announcements in a negative light, the price of our common stock could be adversely affected. Such litigation or proceedings could substantially increase our operating losses and reduce our resources available for development activities. We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their substantially greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have an adverse effect on our ability to compete in the marketplace.

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

We cannot guarantee that any of our or our licensors' patent searches or analyses, including but not limited to the identification of relevant patents, the scope of patent claims or the expiration of relevant patents, are complete or thorough, nor can we be certain that we have identified each and every third-party patent and pending application in the United States, Europe and elsewhere that is relevant to or necessary for the commercialization of our product candidates in any jurisdiction. For example, in the United States, applications filed before November 29, 2000 and certain applications filed after that date that will not be filed outside the United States remain confidential until patents issue. Patent applications in the United States, EU and elsewhere are published approximately 18 months after the earliest filing for which priority is claimed, with such earliest filing date being commonly referred to as the priority date. Therefore, patent applications covering our future product candidates, or their manufacture or use may currently be unpublished. Additionally, pending patent applications that have been published can, subject to certain limitations, be later amended in a manner that could cover our product candidates or the use of our product candidates. The scope of a patent claim is determined by an interpretation of the law, the written disclosure in a patent and the patent's prosecution history. Our interpretation of the relevance or the scope of a patent or a pending application may be incorrect, which may negatively impact our ability to market

our product candidates. We may incorrectly determine that our product candidates are not covered by a third-party patent or may incorrectly predict whether a third party's pending application will issue with claims of relevant scope. Our determination of the expiration date of any patent in the United States, the EU or elsewhere that we consider relevant may be incorrect, which may negatively impact our ability to develop and market our product candidates. Our failure to identify and correctly interpret relevant patents may negatively impact our ability to develop and market our product candidates.

From time to time we may identify patents or applications in the same general area as our products and product candidates. We may determine these third-party patents are irrelevant to our business based on various factors including our interpretation of the scope of the patent claims and our interpretation of when the patent expires. If the patents are asserted against us, however, a court may disagree with our determinations. Further, while we may determine that the scope of claims that will issue from a patent application does not present a risk, it is difficult to accurately predict the scope of claims that will issue from a patent application, our determination may be incorrect, and the issuing patent may be asserted against us. We cannot guarantee that we will be able to successfully settle or otherwise resolve such infringement claims. If we fail in any such dispute, in addition to being forced to pay monetary damages, we may be temporarily or permanently prohibited from commercializing our product candidates. We might, if possible, also be forced to redesign our product candidates so that we no longer infringe on the third-party intellectual property rights. Any of these events, even if we were ultimately to prevail, could require us to divert substantial financial and management resources that we would otherwise be able to devote to our business.

***Changes in patent laws or patent jurisprudence could diminish the value of patents in general, thereby impairing our ability to protect our product candidates.***

As is the case with other biopharmaceutical and pharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical and pharmaceutical industries involve both technological complexity and legal complexity. Therefore, obtaining and enforcing biopharmaceutical and pharmaceutical patents is costly, time-consuming and inherently uncertain. In addition, the America Invents Act ("AIA") which was passed in September 2011, resulted in significant changes to the U.S. patent system.

An important change introduced by the AIA is that, as of March 16, 2013, the United States transitioned to a "first-to-file" system for deciding which party should be granted a patent when two or more patent applications are filed by different parties claiming the same invention. A third party that files a patent application in the USPTO after that date but before us could therefore be awarded a patent covering an invention of ours even if we made the invention before it was made by the third party. This will require us to be cognizant going forward of the time from invention to filing of a patent application, but circumstances could prevent us from promptly filing patent applications on our inventions.

Among some of the other changes introduced by the AIA are changes that limit where a patentee may file a patent infringement suit and provide opportunities for third parties to challenge any issued patent with the USPTO. This applies to all of our U.S. patents, even those issued before March 16, 2013. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in U.S. federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action.

Accordingly, a third party may attempt to use the USPTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action. It is not clear what, if any, impact the AIA will have on the operation of our business. However, the AIA and its implementation could increase the uncertainties and costs surrounding the prosecution of our or our licensors' patent applications and the enforcement or defense of our or our licensors' issued patents.

Additionally, the U.S. Supreme Court has ruled on several patent cases in recent years either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by Congress, the federal courts and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future. Similarly, the complexity and uncertainty of European patent laws has also increased in recent years. In addition, the European patent system is relatively stringent in the type of amendments that are allowed

during prosecution. Changes in patent law and regulations in other countries or jurisdictions or changes in the governmental bodies that enforce them or changes in how the relevant governmental authority enforces patent laws or regulations may weaken our ability to obtain new patents or to enforce patents that we have licensed or that we may obtain in the future. Complying with these laws and regulations could limit our ability to obtain new patents in the future that may be important for our business.

***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 and annuity fees on any issued patent are due to be paid to the USPTO and European and other patent agencies over the lifetime of a patent. In addition, the USPTO and European and other patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. While an inadvertent failure to make payment of such fees or to comply with such provisions can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which such noncompliance will result in the abandonment or lapse of the patent or patent application, and the partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents within prescribed time limits. If we or our licensors fail to maintain the patents and patent applications covering our product candidates or if we or our licensors otherwise allow our patents or patent applications to be abandoned or lapse, our competitors might be able to enter the market, which would hurt our competitive position and could impair our ability to successfully commercialize our product candidates in any indication for which they are approved.

***We enjoy only limited geographical protection with respect to certain patents and we may not be able to protect our intellectual property rights throughout the world.***

Filing, prosecuting and defending patents covering our product candidates in all countries throughout the world would be prohibitively expensive. Competitors may use our and our licensors' 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 and our licensors have patent protection, but enforcement is not as strong as that in the United States or the EU. These products may compete with our product candidates, and our and our licensors' patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

In addition, we may decide to abandon national and regional patent applications before grant. The grant proceeding of each national or regional patent is an independent proceeding which may lead to situations in which applications might in some jurisdictions be refused by the relevant patent offices, while granted by others. Furthermore, the requirements for patentability differ in certain jurisdictions and countries. For example, unlike other countries, China has a heightened requirement for patentability, and specifically requires a detailed description of medical uses of a claimed drug. Furthermore, generic drug manufacturers or other competitors may challenge the scope, validity or enforceability of our or our licensors' patents, requiring us or our licensors to engage in complex, lengthy and costly litigation or other proceedings. Generic drug manufacturers may develop, seek approval for and launch generic versions of our products. It is also quite common that depending on the country, the scope of patent protection may vary for the same product candidate or technology. The laws of some jurisdictions do not protect intellectual property rights to the same extent as the laws or rules and regulations in the United States and the EU, and many companies have encountered significant difficulties in protecting and defending such rights in such 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, 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. Many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. Prosecution of patent applications in other jurisdictions is often a longer process and patents may grant at a later date, and with a shorter term, than in the United States.

Proceedings to enforce our patent rights in other jurisdictions, whether or not successful, 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. We may not be able to prevent third parties from practicing our or our licensors' inventions in all countries outside the United States, or from selling or importing products made using our intellectual property in and into the United States or other jurisdictions. Furthermore, while we intend to protect our intellectual property rights in our expected significant markets, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our product candidates. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate, which may have an adverse effect on our ability to successfully commercialize our product candidates in all of our expected significant foreign markets. If we or our licensors encounter difficulties in protecting, or are otherwise precluded from effectively protecting, the intellectual property rights important for our business in such jurisdictions, the value of these rights may be diminished, and we may face additional competition from others in those jurisdictions.

***If we do not obtain patent term extension in the United States under the Hatch-Waxman Act and in foreign countries under similar legislation, thereby potentially extending the term of marketing exclusivity for our product candidates, our business may be materially harmed.***

Patents have a limited lifespan. In the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional filing date. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired for a product, we may be open to competition from competitive medications, including generic medications. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such 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. If we do not have sufficient patent life to protect our products, our business, financial condition, results of operations, and prospects will be adversely affected.

Depending upon the timing, duration and conditions of FDA marketing approval of our product candidates, we may be able to extend the term of a patent covering each product candidate under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments and similar legislation in the EU. The Hatch-Waxman Amendments permit a patent term extension of up to five years for a patent covering an approved product as compensation for effective patent term lost during product development and the FDA regulatory review process. The total patent term including the extension cannot exceed 14 years following regulatory approval. However, we may not receive an extension if we fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Moreover, the length of the extension could be less than we request. If we are unable to obtain patent term extension or the term of any such extension is less than we request, the period during which we can enforce our patent rights for that product will be shortened and our competitors may obtain approval to market competing products sooner. As a result, our revenue from applicable products could be reduced, possibly materially.

Further, under certain circumstances, patent terms covering our products or product candidates may be extended for time spent during the pendency of the patent application in the USPTO, referred to as Patent Term Adjustment ("PTA"). The laws and regulations underlying how the USPTO calculates the PTA is subject to change and any such PTA granted by the USPTO could be challenged by a third-party. If we do not prevail under such a challenge, the PTA may be reduced or eliminated, resulting in a shorter patent term, which may negatively impact our ability to exclude competitors. Because PTA added to the term of patents covering pharmaceutical products has particular value, our business may be adversely affected if the PTA is successfully challenged by a third party and our ability to exclude competitors is reduced or eliminated.

***Intellectual property rights do not address all potential threats to our competitive advantage.***

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

- others may be able to make products that are similar to Buntanetap or our future product candidates but that are not covered by the claims of the patents that we own or license from others;

- others may independently develop similar or alternative technologies or otherwise circumvent any of our technologies without infringing our intellectual property rights;
- we or any of our collaborators might not have been the first to conceive and reduce to practice the inventions covered by the patents or patent applications that we own, license or will own or license;
- we or any of our collaborators might not have been the first to file patent applications covering certain of the patents or patent applications that we or they own or have obtained a license, or will own or will have obtained a license;
- it is possible that our pending patent applications will not lead to issued patents;
- issued patents that we own may not provide us with any competitive advantage, or may be held invalid or unenforceable, as a result of legal challenges by our competitors;
- our competitors might conduct research and development activities in countries where we do not have patent rights, or in countries where research and development safe harbor laws exist, and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- ownership of our patents or patent applications may be challenged by third parties; and
- the patents of third parties or pending or future applications of third parties, if issued, may have an adverse effect on our business.

***Our reliance on third parties requires us to share our trade secrets, which increases the possibility that our trade secrets will be misappropriated or disclosed, and confidentiality agreements with employees and third parties may not adequately prevent disclosure of trade secrets and protect other proprietary information.***

In addition to seeking patent protection for our product candidates and proprietary technologies, we may also rely on trade secret protection and confidentiality agreements to protect our unpatented know-how, technology, and other proprietary information and to maintain our competitive position. We consider proprietary trade secrets or confidential know-how and unpatented know-how to be important to our business. We may rely on trade secrets or confidential know-how to protect our technology, especially where patent protection is believed by us to be of limited value. Because we expect to rely on third parties to manufacture Buntanetap and any future product candidates, and we expect to collaborate with third parties on the development of Buntanetap and any future product candidates, we must, at times, share trade secrets with them. 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. However, trade secrets or confidential know-how can be difficult to maintain as confidential.

To protect this type of information against disclosure or appropriation by competitors, our policy is to require our employees, consultants, contractors and advisors to enter into confidentiality agreements and, if applicable, material transfer agreements, consulting agreements or other similar agreements with us 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, including our trade secrets. However, current or former employees, consultants, contractors and advisers may unintentionally or willfully disclose our confidential information to competitors, and confidentiality agreements may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. Furthermore, we cannot guarantee that we have entered into applicable agreements with each party that may have or have had access to any potential trade secrets or proprietary technology and processes. 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 an adverse effect on our business and results of operations. Enforcing a claim that a third party obtained illegally and is using trade secrets or confidential know-how is expensive, time consuming and unpredictable. The enforceability of confidentiality agreements may vary from jurisdiction to jurisdiction.

In addition, these agreements typically restrict the ability of our advisors, employees, third-party contractors and consultants to publish data potentially relating to our trade secrets, although our agreements may contain certain limited publication rights. Despite

our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of our agreements with third parties, independent development or publication of information by any of our third-party collaborators. If any of our potential trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business.

***We have not yet registered our trademarks in the United States or other jurisdictions. Failure to secure such registrations could adversely affect our business.***

We have not yet registered our trademarks in the United States or other jurisdictions. If we do not successfully register our trademarks, we may encounter difficulty in enforcing, or be unable to enforce, our trademark rights against third parties, which could adversely affect our business and our ability to effectively compete in the marketplace. We have also not yet registered trademarks for any of our product candidates in any jurisdiction. When we file registration applications for trademarks relating to our product candidates, those applications may be rejected, and registered trademarks may not be obtained, maintained or enforced. During trademark registration proceedings in the United States and foreign jurisdictions, we may receive rejections. We are given an opportunity to respond to those rejections, but we may not be able to overcome such rejections. In addition, in the USPTO and in comparable agencies in many foreign jurisdictions, third parties may oppose pending trademark registration applications or seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademark registrations may not survive such proceedings.

In addition, any proprietary name we may propose to use with Buntanetap or any future product candidate in the United States must be approved by the FDA, regardless of whether we have registered, or applied to register, the proposed proprietary name as a trademark. The FDA typically conducts a review of proposed product names, including an evaluation of potential for confusion with other product names. If the FDA or an equivalent administrative body in a foreign jurisdiction objects to any of our proposed proprietary product names, we may be required to expend significant additional resources in an effort to identify a suitable substitute name that would qualify under applicable trademark laws, not infringe, misappropriate or otherwise violate the existing rights of third parties and be acceptable to the FDA.

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

Our unregistered trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on, misappropriating or violating other marks. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential collaborators or customers in our markets of interest. During trademark registration proceedings, we may receive rejections of our applications by the USPTO or in other foreign jurisdictions. Although we are given an opportunity to respond to such rejections, we may be unable to overcome them. At times, competitors may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, in the USPTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. There could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our unregistered trademarks or trade names. Furthermore, in many countries, owning and maintaining a trademark registration may not provide an adequate defense against a subsequent infringement claim asserted by the owner of a senior trademark. Over the long term, if we are unable to successfully register our trademarks and trade names and establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively, and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade names, domain names or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely impact our financial condition or results of operations.

***In response to an inability to enforce our patent rights, or in the event of successful litigation against us by third parties, or in the normal course of future business operations, we may need to license certain intellectual property from third parties, and such licenses may not be available or may not be available on commercially reasonable terms.***

As a result of patent infringement claims, or in order to avoid potential infringement claims, we may choose to seek, or be required to seek, a license from the third party, which may require us to pay license fees or royalties or both. Furthermore, if we or our licensors are unsuccessful in any proceedings sought to enforce our patent rights, such patents and patent applications may be

narrowed, invalidated or held unenforceable, we may be required to obtain licenses from third parties. Although at this time, we are unaware of any intellectual property that interferes with ours or is complementary and needed to commercialize Buntanetap, a third party may also hold intellectual property, including patent rights that are important or necessary to the future development or commercialization of Buntanetap or our future product candidates. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize Buntanetap or our product candidates, in which case we would be required to obtain a license from these third parties. If any of these situations were to occur, such a license may not be available on commercially reasonable terms, or at all, which could materially harm our business. Even if a license can be obtained on acceptable terms, the rights may be nonexclusive, which could give our competitors access to the same intellectual property rights. If we are unable to enter into a license on acceptable terms, we could be prevented from commercializing one or more of our product candidates, forced to modify such product candidates, or to cease some aspect of our business operations, which could harm our business significantly.

***We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of their former employers or other third parties or claims asserting ownership of what we regard as our own intellectual property.***

We employ individuals who were previously employed at other biotechnology or pharmaceutical companies. Although we seek to protect our ownership of intellectual property rights by ensuring that our agreements with our employees, contractors, collaborators and other third parties with whom we do business include provisions requiring such parties to assign rights in inventions to us and 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 confidential information of our employees' former employers or other third parties. In addition, while it is our policy to require our employees and contractors who may be involved in the conception or development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, conceives or develops intellectual property that we regard as our own. The assignment of intellectual property rights may not be self-executing, or the assignment agreements may be breached, and we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property. We may also be subject to claims that former employers or other third parties have an ownership interest in our patents. Litigation may be necessary to defend against any of the foregoing claims. There is no guarantee of success in defending these claims, and 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 or right to use. Even if we are successful, litigation could result in substantial cost and be a distraction to our management and other employees.

***Our proprietary information may be lost, or we may suffer security breaches.***

In the ordinary course of our business, we collect and store sensitive data, including intellectual property, clinical trial data, proprietary business information, personal data and personally identifiable information of our clinical trial subjects and employees, in our data centers and on our networks. The secure processing, maintenance and transmission of this information is critical to our operations. Despite our security measures, our information technology and infrastructure may be vulnerable to attacks by hackers or breached due to employee error, malfeasance or other disruptions. Certain federal, state and foreign government requirements include obligations of companies to notify individuals of security breaches involving particular categories of personally identifiable information, which could result from breaches experienced by us or by our vendors, contractors, or organizations with which we have formed strategic relationships. Although, to our knowledge, we have not experienced any such material security breach to date, any such breach could compromise our networks and the information stored there could be accessed, publicly disclosed, lost or stolen. Any such access, disclosure or other loss of information could result in legal claims or proceedings, liability under laws that protect the privacy of personal information, significant regulatory penalties, disruption of our operations, delays in our regulatory approval efforts, damage to our reputation, costs to recover or reproduce the data and cause a loss of confidence in us and our ability to conduct clinical trials, which could adversely affect our reputation and delay our clinical development of our product candidates.

If any security breach or other incident, whether actual or perceived, were to occur, it could impact our reputation and/or operations, cause us to incur significant costs and liabilities, including legal expenses, harm customer confidence, hurt our expansion into new markets, cause us to incur remediation costs, or cause us to lose existing customers. For example, the loss of clinical trial data from clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. We also rely on third parties to manufacture Buntanetap, and similar events relating to their computer systems could also have a material adverse effect on our business. To the extent that any actual or perceived disruption or security breach affects our systems (or those of our third-party collaborators, service providers, contractors or consultants) or were to result in a loss of

or accidental, unlawful or unauthorized access to, use of, release of, or other processing of personally identifiable information, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, the further development and commercialization of Buntanetap or any future product candidates could be delayed, and we could be subject to significant fines, penalties or liabilities. In addition, a security failure could result in violations of applicable privacy and other laws. If this information is inappropriately accessed and used by a third party or a team member for illegal purposes, such as identity theft, we may be responsible to the affected individuals for any losses they may have incurred as a result of misappropriation. In such an instance, we may also be subject to regulatory action, investigation or liable to a governmental authority for fines or penalties associated with a lapse in the integrity and security of our team members' or patients' information. We may be required to expend significant capital and other resources to protect against and remedy any potential or existing security breaches and their consequences. In addition, our remediation efforts may not be successful and we may not have adequate insurance to cover these losses.

Security breaches could also significantly damage our brand and our reputation with existing and prospective clients and third parties with whom we do business. Any publicized security problems affecting our businesses and/or those of such third parties may negatively impact the market perception of our products and discourage third parties from doing business with us.

### **Risks Related to Our Employees, Managing Our Growth and Our Operations**

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

We are highly dependent on the development, regulatory, commercialization and business development expertise of Maria L. Maccacchini, PhD, as well as the other principal members of our management, scientific and clinical teams. Although we have employment agreements, offer letters or consulting agreements with our executive officers, these agreements do not prevent them from terminating their services at any time.

If we lose one or more of our executive officers or key employees, our ability to implement our business strategy successfully could be seriously harmed. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop product candidates, gain regulatory approval, and commercialize new products. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these additional key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be engaged by entities other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us.

Other pharmaceutical companies with which we compete for qualified personnel have greater financial and other resources, different risk profiles, and a longer history in the industry than we do. They also may provide more diverse opportunities and better chances for career advancement. Some of these characteristics may be more appealing to high-quality candidates than what we have to offer. If we are not able to attract, integrate, retain and motivate necessary personnel to accomplish our business objectives, we may experience constraints that will significantly impede the achievement of our development objectives, our ability to raise additional capital and our ability to implement our business strategy.

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

We expect to experience significant growth in the number of our employees and the scope of our operations. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities or acquire new facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.



***We may engage in acquisitions that could disrupt our business, cause dilution to our stockholders or reduce our financial resources.***

In the future, we may enter into transactions to acquire other businesses, products or technologies. If we do identify suitable candidates, we may not be able to make such acquisitions on favorable terms, or at all. Any acquisitions we make may not strengthen our competitive position, and these transactions may be viewed negatively by customers or investors. We may decide to incur debt in connection with an acquisition or issue our common stock or other equity securities to the stockholders of the acquired company, which would reduce the percentage ownership of our existing stockholders. We could incur losses resulting from undiscovered liabilities of the acquired business that are not covered by the indemnification we may obtain from the seller. In addition, we may not be able to successfully integrate the acquired personnel, technologies and operations into our existing business in an effective, timely and nondisruptive manner. Acquisitions may also divert management attention from day-to-day responsibilities, increase our expenses and reduce our cash available for operations and other uses. We cannot predict the number, timing or size of future acquisitions or the effect that any such transactions might have on our operating results. Furthermore, we may experience losses related to investments in other companies, including as a result of failure to realize expected benefits or the materialization of unexpected liabilities or risks, which could have a material negative effect on our results of operations and financial condition. Accordingly, although there can be no assurance that we will undertake or successfully complete any additional transactions of the nature described above, any additional transactions that we do complete could have a material adverse effect on our business, results of operations, financial condition and prospects.

***We may seek to enter into collaborations, license agreements and other similar arrangements in the future, and may not be successful in doing so.***

We may seek to enter into collaborations, joint ventures, licensing arrangements or other similar arrangements with third parties for the development or commercialization of Buntanetap and any future product candidates, due to capital costs required to develop or commercialize the product candidate or manufacturing constraints. These relationships or those like them may require us to incur non-recurring and other charges, increase our near- and long-term expenditures, issue securities that dilute our stockholders or disrupt our management and business. In addition, we face significant competition in seeking appropriate strategic partners and the negotiation process is time-consuming and complex. Moreover, we may not be successful in our efforts to establish or maintain a strategic partnership or other alternative arrangements for any future product candidates and programs because our research and development pipeline may be insufficient, our product candidates and programs may be deemed to be at too early a stage of development for collaborative effort and third parties may not view our product candidates and programs as having the requisite potential to demonstrate safety and efficacy. Even if we are successful in our efforts to establish such collaborations, the terms that we agree upon may not be favorable to us. For example, we may need to relinquish valuable rights to our future revenue streams, research programs, intellectual property or product candidates, or grant licenses on terms that may not be favorable to us, as part of any such arrangement, and such arrangements may restrict us from entering into additional agreements with other potential collaborators. If we license products or businesses, we may not be able to realize the benefit of such transactions if we are unable to successfully integrate them with our existing operations and company culture. In addition, if we enter into such collaborations, we will have limited control over the amount and timing of resources that our collaborators will dedicate to the development or commercialization of our product candidates. Our ability to generate revenue from these arrangements will depend on any future collaborators' abilities to successfully perform the functions assigned to them in these arrangements. We cannot be certain that, following a strategic transaction or license, we will achieve the revenues or specific net income that justifies such transaction. Furthermore, we may not be able to maintain such collaborations if, for example, the development or approval of a product candidate is delayed, the safety of a product candidate is questioned or the sales of an approved product candidate are unsatisfactory. Any delays in entering into new strategic partnership agreements related to our drug candidates could also delay the development and commercialization of our product candidates and reduce their competitiveness even if they reach the market.

Collaborations involving Buntanetap or any future product candidates would pose significant risks to us, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected or at all;

- we could grant exclusive rights to our collaborators that would prevent us from collaborating with others;
- collaborators may not pursue development and commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or drugs, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;
- a collaborator with marketing and distribution rights to any product candidate that achieves regulatory approval may not commit sufficient resources to the marketing and distribution of such products;
- a collaborator's sales and marketing activities or other operations may not be in compliance with applicable laws, resulting in civil or criminal proceedings;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays in or termination of the research, development or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time-consuming and expensive;
- collaborators may not properly enforce, maintain or defend our or their intellectual property rights or may use our or their proprietary information in such a way as to invite litigation that could jeopardize or invalidate such intellectual property or proprietary information or expose us to potential litigation;
- collaborators may infringe, misappropriate or otherwise violate the intellectual property rights of third parties, which may expose us to litigation and potential liability;
- collaborators may not provide us with timely and accurate information regarding development, regulatory or commercialization status or results, which could adversely impact our ability to manage our own development efforts, accurately forecast financial results or provide timely information to our stockholders regarding our out-licensed product candidates;
- we may be required to invest resources and attention into such collaboration, which could distract from other business objectives;
- disputes may arise between the collaborators and us regarding ownership of or other rights in the intellectual property generated in the course of the collaborations;
- collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all;
- if a collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program could be delayed, diminished or terminated; and

- collaborations may be terminated, including for the convenience of the collaborator, prior to or upon the expiration of the agreed upon terms and, if terminated, we may find it more difficult to enter into future collaborations or be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

Any termination of collaborations we enter into in the future, or any delay in entering into collaborations related to Buntanetap or any future product candidates, could delay the development and commercialization of our product candidates and reduce their competitiveness if they reach the market, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

***Our business and operations would suffer in the event of failures involving our information technology systems, or those of any of our service providers.***

We are increasingly dependent upon information technology systems, infrastructure and data to operate our business. Our computer systems, as well as those of our CROs and other contractors and consultants, are vulnerable to damage from computer viruses, unauthorized access, natural disasters (including hurricanes), team member misconduct, human error, terrorism, war and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs. For example, the loss of preclinical or clinical trial data from completed, ongoing or planned trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of or damage to our data or applications, or inappropriate disclosure of personal, confidential or proprietary information, we could incur liability and the further development of Buntanetap or any other product candidate could be delayed. It is not possible to prevent all threats to our information technology systems and information and those of our third-party service providers, over which we exert less control, and any controls we implement to do so may prove to be ineffective.

***The cash and cash equivalents that we use to meet our working capital and operating expense needs are held in deposit accounts at two financial institutions. If one or both financial institutions fail, our deposit accounts could be adversely affected due to the loss of or delay in obtaining access to all or a portion of our uninsured funds.***

The cash and cash equivalents that we use to meet our working capital and operating expense needs are held in deposit accounts at two financial institutions. The balance held in these accounts regularly exceeds the Federal Deposit Insurance Corporation (“FDIC”), standard deposit insurance limit or similar government guarantee schemes. If one or both of the financial institutions in which we hold such funds fails or is subject to significant adverse conditions in the financial or credit markets, we could be subject to a risk of loss of all or a portion of such uninsured funds or be subject to a delay in accessing all or a portion of such uninsured funds. Any such loss or lack of access to these funds could adversely impact our short-term liquidity and ability to meet our operating expense obligations.

For example, on March 10, 2023, Silicon Valley Bank (“SVB”) and Signature Bank, were closed by state regulators and the FDIC was appointed as the receiver for each bank. The FDIC created successor bridge banks and all deposits of SVB and Signature Bank were transferred to the bridge banks under a systemic risk exception approved by the U.S. Department of the Treasury, the Federal Reserve and the FDIC. If one or both of the financial institutions in which we hold our funds for working capital and operating expense needs were to fail, we cannot provide any assurances that such governmental agencies would take action to protect our uninsured deposits in a similar manner.

## **Risks Related to Our Common Stock**

***The market price of our common stock has been volatile and fluctuated substantially in the past, and may continue to experience volatility and substantial fluctuations in the future, which could result in substantial losses for purchasers of our common stock.***

The market price of our common stock is highly volatile. For example, from August 1, 2022 to March 30, 2023, the sale price of our common stock on the New York Stock Exchange ranged from as low as \$9.84 to as high as \$23.91 and daily trading volume ranged from 5,000 shares to 768,700 shares. The market price of our common stock may be subject to wide fluctuations in response to a variety of factors, including the following:

- results of our clinical trials, and the results of trials of our competitors or those of other companies in our market sector;

- our ability to enroll subjects in our future clinical trials;
- delays or unanticipated developments in the completion of our planned clinical trials;
- any delay in submitting an NDA and any adverse development or perceived adverse development with respect to the FDA's review of that NDA;
- our ability to obtain and maintain regulatory approval of Buntanetap or any future product candidates or additional indications thereof, or limitations to specific label indications or patient populations for its use, or changes or delays in the regulatory review process;
- failure to successfully develop and commercialize Buntanetap or any future product candidates;
- the degree and rate of physician and market adoption of any of our current and future product candidates;
- inability to obtain additional funding or obtaining funding on unattractive terms;
- regulatory or legal developments in the United States and other countries applicable to Buntanetap or any other product candidates;
- adverse regulatory decisions;
- changes in the structure of healthcare payment systems;
- manufacturing, supply or distribution delays or shortages, including our inability to obtain adequate product supply for Buntanetap or any other product candidates, or the inability to do so at acceptable prices;
- the success or failure of our efforts to identify, develop, acquire or license additional product candidates;
- introduction of new products, services or technologies by our competitors;
- failure to meet or exceed financial projections we provide to the public;
- failure to meet or exceed the estimates and projections of the investment community;
- changes in the market valuations of companies similar to ours;
- market conditions in the pharmaceutical and biotechnology sectors, and the issuance of new or changed securities analysts' reports or recommendations;
- announcements of significant acquisitions, strategic collaborations, joint ventures or capital commitments by us or our competitors;
- any changes to our relationship with any manufacturers, suppliers, collaborators or other strategic partners;
- significant lawsuits, including patent or shareholder litigation, and disputes or other developments relating to our 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;
- sales of our common stock by us or our stockholders in the future;

- changes in our capital structure, such as future issuances of securities and the incurrence of additional debt;
- changes in accounting standards, policies, guidelines, interpretations or principles;
- trading volume of our common stock;
- actual or anticipated fluctuations in our financial condition and results of operations;
- publication of news releases by other companies in our industry, and especially direct competitors, including about adverse developments related to safety, effectiveness, accuracy and usability of their products, reputational concerns, reimbursement coverage, regulatory compliance, and product recalls;
- general economic, industry and market conditions, including but not limited to the impact of the COVID-19 pandemic;
- announcement or progression of geopolitical events (including in relation to the conflict between Russia and Ukraine); and
- the other factors described in this “Risk Factors” section.

In addition, the stock markets have experienced extreme price and volume fluctuations that have affected and continue to affect the market prices of equity securities of many companies. These fluctuations have often been unrelated or disproportionate to the operating performance of those companies. Broad market and industry factors, as well as general economic, political, regulatory and market conditions, may negatively affect the market price of our common stock, regardless of our actual operating performance. The market price of our common stock may decline, and our stockholders may lose some or all of their investment.

***Our failure to meet the New York Stock Exchange’s continued listing requirements could result in a delisting of our common stock.***

If we fail to satisfy the continued listing requirements of the New York Stock Exchange, such as the corporate governance requirements or the minimum closing bid price requirement, the New York Stock Exchange may take steps to delist our common stock. Such a delisting would likely have a negative effect on the price of our common stock and would impair our stockholders’ ability to sell or purchase our common stock when they wish to do so. In the event of a delisting, we can provide no assurance that any action taken by us to restore compliance with listing requirements would allow our common stock to become listed again, stabilize the market price or improve the liquidity of our common stock, or prevent future non-compliance with the listing requirements of the New York Stock Exchange.

***We have been subject to securities class action litigation in the past, and could be subject to such litigation in the future.***

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 biotechnology companies have experienced significant share price volatility in recent years. During the year ended December 31, 2021, two securities class action complaints were filed against us and our executive officers following disclosure of interim results from the AD/PD Trials. Both complaints were voluntarily dismissed without prejudice by the plaintiffs. If we again face such litigation in the future, it could result in substantial costs, a diversion of management’s attention and resources, and damage to our reputation, which could have a material adverse effect on our business, financial condition and results of operations and prospects.

***Our directors, executive officers and certain stockholders own a significant percentage of our common stock and, if they choose to act together, will be able to exert significant control over matters subject to stockholder approval.***

Our directors, executive officers, and stockholders affiliated with our directors and executive officers own approximately 30.9% of the current voting power of our outstanding common stock. Therefore, acting together, they have the ability to substantially influence all matters submitted to our board of directors or stockholders for approval. For example, these holders may be able to control the appointment of our management, elections and removal of directors, amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. The interests of these holders may not always coincide

with our corporate interests or the interests of other stockholders, and they may act in a manner with which our stockholders may not agree or that may not be in the best interests of our other stockholders. This concentration of ownership may have the effect of delaying, deferring or preventing a change in control, impeding a merger, consolidation, takeover or other business combination involving us, or discouraging a potential acquiror from making a tender offer or otherwise attempting to obtain control of our business, even if such a transaction would benefit other stockholders. So long as they continue to own a significant amount of our equity, these holders will be able to strongly influence or effectively control our decisions.

***If securities or industry analysts do not publish research or reports about our business, or if they issue an adverse or misleading opinion regarding our common stock, our stock price and trading volume could decline.***

The trading market for our common stock depends, in part, on the research and reports that securities or industry analysts may publish about us, our business, our market or our competitors. We do not have any control over these analysts. If our financial performance fails to meet analyst estimates or one or more of the analysts who cover us downgrade our common stock or change their opinion of our common stock, our share price would likely decline. If one or more of these analysts cease coverage of us or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our share price or trading volume to decline.

***Because we do not anticipate paying any cash dividends on our common stock in the foreseeable future, capital appreciation, if any, will be sole source of gain for our stockholders.***

We have never declared or paid any cash dividends on our common stock. We currently 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. In addition, any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock would be our stockholders' sole source of gain on an investment in our common stock for the foreseeable future. There is no guarantee that shares of our common stock will appreciate in value or even maintain the price at which stockholders have purchased their shares. See "Dividend Policy" for additional information.

***We identified a material weakness in our internal control over financial reporting, which resulted in the restatement of our financial statements for several prior quarterly and year-to-date periods. If remediation of this material weakness is not effective, or if we fail to maintain an effective system of internal control over financial reporting in the future, we may not be able to accurately or timely report our financial condition or operating results, which may adversely affect investor confidence in our company and, as a result, the value of our common stock.***

We identified a material weakness in our internal control over financial reporting as of February 23, 2023. As defined in the standards established by the U.S. Public Company Accounting Oversight Board, a "material weakness" is a deficiency, or combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of our company's annual or interim financial statements will not be prevented, or detected on a timely basis.

The material weakness identified related to the proper classification of research and development expenses, which impacted our previously issued condensed financial statements as of and for the three months ended March 31, 2022, three and six months ended June 30, 2022 and three and nine months ended September 30, 2022. As further described in note 12 to our financial statements included elsewhere in this Annual Report on Form 10-K, there were material amounts inappropriately classified as research and development expense which should have been classified as prepaid assets and other assets. We are taking steps to remediate the material weakness and are in the process of supplementing our existing internal controls related to the proper classification of research and development expenses. In response to the material weakness, we are enhancing our review procedures over significant contracts with contract manufacturing organizations and contract research organizations, augmenting existing staff and strengthening our review process. The incremental internal controls created to respond to this material weakness are being integrated into our internal controls testing plan and they will be tested during 2023.

Although we plan to complete the above remediation process and associated evaluation and testing as quickly as possible, we may not be able to do so and our initiatives may prove not to be successful. If our remedial measures are insufficient to address the material weakness, or if additional material weaknesses or significant deficiencies in our internal control over financial reporting are discovered during the evaluation and testing process, we will be unable to assert that our internal control over financial reporting is effective and our independent registered public accounting firm will be unable to express an opinion on the effectiveness of our

internal control. If we fail to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, shareholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our common stock.

***The restatement of our prior quarterly financial statements may affect investor confidence and raise reputational issues and may subject us to additional risks and uncertainties, including increased professional costs and the increased possibility of legal proceedings and regulatory inquiries.***

As discussed in note 12 to our financial statements included elsewhere in this Annual Report on Form 10-K, we determined to restate our condensed financial statements as of and for the three months ended March 31, 2022, three and six months ended June 30, 2022 and three and nine months ended September 30, 2022 after we identified material amounts inappropriately classified as research and development expense which should have been classified as prepaid assets and other assets. As a result of this error and the resulting restatement of our condensed financial statements for the impacted periods, we have incurred, and may continue to incur, unanticipated costs for accounting and legal fees in connection with or related to the restatement, and have become subject to a number of additional risks and uncertainties, including the increased possibility of litigation and regulatory inquiries. Any of the foregoing may affect investor confidence in the accuracy of our financial disclosures and may raise reputational risks for our business, both of which could harm our business and financial results.

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

As a public company, and particularly after we no longer qualify as an emerging growth company, we incur significant legal, accounting and other expenses. The Sarbanes-Oxley Act of 2002 (“SOX”), the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of the New York Stock Exchange, and other applicable securities rules and regulations impose various requirements on U.S. reporting public companies, including the establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations increase our legal and financial compliance costs and make some activities more time-consuming and costly. For example, these rules and regulations may make it more expensive for us to obtain director and officer liability insurance, which in turn could make it more difficult for us to attract and retain qualified senior management personnel or members for our board of directors. In addition, these rules and regulations are often subject to varying interpretations, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices. Pursuant to Section 404 of SOX, we are required to furnish a report by our senior management on our internal control over financial reporting. While we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm.

To comply with Section 404, we are required to engage in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we need to continue to dedicate internal resources, engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and maintain a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by Section 404. We have had a material weakness in our internal control over financial reporting in the past, and cannot assure you that there will not be material weaknesses or significant deficiencies in our internal control over financial reporting in the future. Any failure to maintain internal control over financial reporting could severely inhibit our ability to accurately report our financial condition, results of operations or cash flows. If we are unable to conclude that our internal control over financial reporting is effective, or if our independent registered public accounting firm determines we have a material weakness or significant deficiency in our internal control over financial reporting once that firm begins its Section 404 reviews, investors may lose confidence in the accuracy and completeness of our financial reports, the market price of our common stock could decline, and we could be subject to sanctions or investigations by the NYSE, SEC or other regulatory authorities. Failure to remedy any material weakness in our internal control over financial reporting, or to implement or maintain other effective control systems required of public companies, could also restrict our future access to the capital markets.

***We are an “emerging growth company,” and the reduced reporting requirements applicable to emerging growth companies may make our common stock less attractive to investors.***

We are an “emerging growth company,” as defined in the Jumpstart Our Business Startups Act (“JOBS Act”). For as long as we continue to be an emerging growth company, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies, including exemption from compliance with the auditor attestation requirements of Section 404, reduced disclosure obligations regarding executive compensation and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved. We will remain an emerging growth company until the earlier of (1) the last day of the fiscal year (a) following the fifth anniversary of the closing of our initial public offering (“IPO”) on January 31, 2020, (b) in which we have total annual gross revenue of at least \$1.07 billion or (c) in which we are deemed to be a large accelerated filer, which means the market value of our common stock held by non-affiliates exceeds \$700 million as of the end of our prior second fiscal quarter, and (2) the date on which we have issued more than \$1.0 billion in non-convertible debt during the prior three-year period.

In addition, under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our share price may be more volatile.

***Provisions in our restated certificate of incorporation and amended and restated bylaws and under Delaware law could make an acquisition of our company, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.***

Provisions in our restated certificate of incorporation and our amended and restated bylaws that became effective upon the closing of our IPO may discourage, delay or prevent a merger, acquisition or other change in control of our company that stockholders may consider favorable, including transactions in which our stockholders might otherwise receive a premium for their shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions include those establishing advance notice bylaw provisions for proposals from stockholders for presentation at annual meetings and forum selection bylaw provisions.

Because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the General Corporation Law of the State of Delaware, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

Furthermore, our restated certificate of incorporation that became effective upon the closing of our IPO specifies that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for most legal actions involving actions brought against us by stockholders. We believe this provision benefits us by providing increased consistency in the application of Delaware law by chancellors particularly experienced in resolving corporate disputes, efficient administration of cases on a more expedited schedule relative to other forums and protection against the burdens of multi-forum litigation. However, the provision may have the effect of discouraging lawsuits against our directors and officers. The enforceability of similar choice of forum provisions in other companies’ certificates of incorporation has been challenged in legal proceedings, and it is possible that, in connection with any applicable action brought against us, a court could find the choice of forum provisions contained in our restated certificate of incorporation to be inapplicable or unenforceable in such action.



*Our bylaws designate the Court of Chancery of the State of Delaware as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by 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 bylaws provide that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware is the exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders with respect to our company and our directors. This choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that the stockholder believes is favorable for disputes with us or our directors, which may discourage meritorious claims from being asserted against us and our directors. Alternatively, if a court were to find this provision of our charter inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could adversely affect our business, financial condition or results of operations. We adopted this provision because we believe it makes it less likely that we will be forced to incur the expense of defending duplicative actions in multiple forums and less likely that plaintiffs' attorneys will be able to employ such litigation to coerce us into otherwise unjustified

**Item 1B. Unresolved Staff Comments.**

None.

**Item 2. Properties.**

Our offices are in Berwyn, Pennsylvania, where we have leased and have access to 1,500 square feet of office space pursuant to a short-term lease agreement. We believe that our facilities are adequate to meet our current needs.

**Item 3. Legal Proceedings.**

From time to time, we may become subject to litigation and claims arising in the ordinary course of business. We are not currently a party to any material legal proceedings, and we are not aware of any pending or threatened legal proceedings against us that we believe could have a material adverse effect on our business, operating results or financial condition.

**Item 4. Mine Safety Disclosures.**

Not applicable.

## PART II

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

#### Market Information

Our common stock is listed on the New York Stock Exchange under the symbol "ANVS". Our common stock began trading on the New York Stock Exchange on November 18, 2021. From January 29, 2020, the date of our initial public offering, to November 17, 2021, our common stock traded on the NYSE American. Prior to January 29, 2020, there was no public market for our stock.

#### Holders of Record

As of March 30, 2022, there were approximately 19 holders of record of shares of our common stock. This number does not reflect the beneficial holders of our common stock who hold shares in street name through brokerage accounts or other nominees.

#### 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.

#### Securities Authorized for Issuance Under Equity Compensation Plans

The information called for by this item regarding equity compensation plans is incorporated by reference to Part III, Item 12 of this Annual Report on Form 10-K.

#### Issuer Purchases of Equity Securities

None.

#### Recent Sales of Unregistered Securities

We did not issue any equity securities during the year ended December 31, 2022 that were not registered under the Securities Act and that have not otherwise been described in a Quarterly Report on Form 10-Q or a Current Report on Form 8-K.

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

*You should read the following discussion and analysis of our financial condition and results of operations together with our financial statements and the related notes appearing at the end of this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. You should read "Cautionary Note Regarding Forward-Looking Statements" and Item 1A. Risk Factors of this Annual Report on Form 10-K for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.*

#### Overview

##### Company Overview

We are a clinical stage, drug platform company addressing neurodegeneration, such as Alzheimer's disease ("AD") and Parkinson's disease ("PD"). We are developing our lead product candidate, Buntanetap, which is designed to address AD, PD and potentially other chronic neurodegenerative diseases. Buntanetap is a synthetically produced small molecule, orally administered, brain penetrant compound. In several studies, Buntanetap was observed to inhibit the synthesis of neurotoxic proteins—APP/A $\beta$  ("APP"), tau/phospho-tau ("tau") and  $\alpha$ -Synuclein (" $\alpha$ SYN")—that are one of the main causes of neurodegeneration. High levels of

neurotoxic proteins lead to impaired axonal transport, which is responsible for the communication between and within nerve cells. When that communication is impaired, the immune system is activated and attacks the nerve cells, eventually killing them. We have observed in our clinical studies in early AD and early PD patients and pre-clinical studies in mice and rats that Buntanetap lowered neurotoxic protein levels leading to improved axonal transport, reduced inflammation, lower nerve cell death and improved affected function.

In 2021, we completed two Phase 1/2 clinical studies: one in 14 early AD patients, and one in 54 early PD patients (together, the “AD/PD Trials”). In the AD/PD Trials, early AD patients were defined as those with a Mini Mental State Examination (MMSE) score between 19 and 28 and early PD patients as those patients at Hoehn & Yahr stages 1, 2 or 3. MMSE is a brief screening instrument used to assess cognitive function, with total scores ranging from 0 to 30 and a lower score indicating greater disease severity, while the Hoehn & Yahr scale is a medical assessment used to measure staging of the functional disability associated with PD where a higher stage indicates greater disease severity. In collaboration with the Alzheimer’s Disease Cooperative Study (“ADCS”), we also conducted a trial in 16 early AD patients (the “ADCS Trial”). In the ADCS Trial, early AD patients were defined as those patients with a MMSE score between 19 and 28. All three clinical trials were double-blind, placebo-controlled studies. We designed the studies by applying our understanding of the underlying neurodegenerative disease states, and measured both target and pathway validation in the spinal fluid of patients to determine whether patients improved following treatment. In addition to meeting their primary endpoints of safety and tolerability and secondary endpoint of pharmacokinetics of Buntanetap, our AD/PD Trials met exploratory endpoints of measures of biomarkers and improvements in cognition in AD patients, and in function in PD patients. We believe that the AD/PD Trials represent the first double-blind placebo-controlled studies that showed improvements in AD patients, as measured by ADAS-Cog, and in PD patients, as measured by UPDRS. Following completion of the AD/PD Trials, we submitted our data to the U.S. Food and Drug Administration (“FDA”) and requested direction to further pursue the development of Buntanetap in early PD patients. With the FDA’s guidance, we initiated a Phase 3 study in early PD patients in August 2022 (our “Phase 3 PD Study”). In the Phase 3 PD Study, early PD patients were defined as those at Hoehn & Yahr stages 1, 2 or 3, and OFF times of less than two hours per day. OFF time refers to when PD motor and/or non-motor symptoms occur between medication doses. We also submitted a proposed protocol for the treatment of moderate AD to the FDA, and after receiving permission to proceed, we initiated a Phase 2/3 study in mild to moderate AD patients in February 2023 (our “Phase 2/3 AD Study”). In the Phase 2/3 AD Study, mild to moderate AD patients were defined as those with a MMSE score between 14 and 24. At the completion of the ADCS Trial, the data showed that Buntanetap is a translational inhibitor in humans just like in animals, and we further observed that there was statistical improvement in cognition in early AD patients, just like in the AD/PD Trials.

Our Phase 3 PD Study and Phase 2/3 AD Study each have built in interim analyses. Our Phase 3 PD Study incorporated an interim analysis at two months, the results of which were disclosed on March 31, 2023. The pre-planned interim analysis was conducted by our data analytics provider based on 132 patients from all cohorts collectively for which baseline and two-month data was available. As the interim analysis was conducted at two months of the six-month endpoint and only on 132 patients, it may not be indicative of the results at six months for the full patient population because as the trial progresses, clinical outcomes may materially change as patient enrollment continues and more patient data become available, or different conclusions or considerations may qualify such results once additional data have been received and fully evaluated. Based on the results of the interim analysis, we intend to proceed with the Phase 3 PD Study as planned in accordance with the previously established protocol. We remain blinded to the Phase 3 PD Study and we do not have safety or efficacy data from the trial. A separate safety interim analysis is in process and we expect that interim analysis to be released in the second quarter of 2023. We intend to disclose the results of an interim analysis for our Phase 2/3 AD Study in Fall 2023. We plan to consult with the FDA following completion of these interim analyses, to obtain feedback on our ongoing and planned AD and PD studies, including conducting an open label extension study following the completion of the initial trials. Using the data from the Phase 3 PD Study interim analysis, we intend to design an 18-month long disease-modifying Phase 3 study in the same early PD patients. In addition, we intend to conduct a short 6-month study in advanced PD patients during the second half of the 18-month disease modifying Phase 3 study, at which time we will define the advanced PD patient population for the purposes of such study. Similarly, using the data from the Phase 2/3 AD Study interim analysis, we intend to design an 18-month disease modifying Phase 3 study in the same early AD patient population. In addition, we intend to conduct a short 6-month study in advanced AD patients during the second half of the 18-month disease modifying Phase 3 study, at which time we will define the advanced AD patient population for the purposes of such study. We expect both the ongoing Phase 3 PD Study and the Phase 2/3 AD Study to be completed by the end of 2023, and we intend to announce the data from the final analyses in the first quarter of 2024.

By the end of 2026, our goal is to have conducted the required pivotal studies for Buntanetap to be able to file two new drug applications (“NDAs”) with the FDA.

We believe that we are the only company developing a drug for AD and PD that is designed to inhibit more than one neurotoxic protein, and has a mechanism of action designed to restore nerve cell axonal and synaptic activity. By improving brain function, our goal is to treat memory loss and dementia associated with AD as well as body and brain function associated with PD. Based on pre-clinical and clinical data collected to date, we believe that Buntanetap has the potential to be the first drug to interfere with the underlying mechanism of neurodegeneration, potentially enabling Buntanetap to be the only drug to improve cognition in AD and motor function in PD. The industry has encountered challenges in specifically targeting one neurotoxic protein, be it APP, tau or  $\alpha$ SYN, indicating that doing so does not change the course of neurodegeneration. Our goal is to develop a disease modifying drug (“DMD”) for patients with neurodegeneration by leveraging our clinical and pre-clinical data to inhibit the three most relevant neurotoxic proteins. Studies have found that AD and PD are the most common neurodegenerative diseases in the U.S., and accordingly these diseases present two unmet needs of the aging population and two potentially large U.S. markets if a DMD is developed and approved.

We have never been profitable and have incurred net losses since inception. Our accumulated deficit at December 31, 2022 was \$54,054,774. We expect to incur losses for the foreseeable future, and we expect these losses to increase as we continue our development of, and seek regulatory approvals for, our product candidates. Because of the numerous risks and uncertainties associated with product development, we are unable to predict the timing or amount of increased expenses or when we will be able to achieve or maintain profitability, if at all.

### ***Financial Operations Overview***

The following discussion sets forth certain components of our statements of operations as well as factors that impact those items.

### ***Research and Development Expenses***

Our research and development expenses consist of expenses incurred in development and clinical studies relating to our product candidates, including:

- expenses associated with clinical development;
- personnel-related expenses, such as salaries, benefits, travel and other related expenses, including stock-based compensation; and
- payments to third-party contract research organizations (“CROs”), contractor laboratories and independent contractors.

Research and development costs are either expensed as incurred or recorded separately as a prepaid asset, and the expense recognized when the service is performed. Clinical development expenses for our product candidates are a significant component of our current research and development expenses. Product candidates in later stage clinical development generally have higher research and development expenses than those in earlier stages of development, primarily due to increased size and duration of the clinical trials. We track and record information regarding external research and development expenses for each study or trial that we conduct. From time to time, we use third-party CROs, contractor laboratories and independent contractors in clinical studies. We recognize the expenses associated with third parties performing these services for us in our clinical studies based on the percentage of each study completed at the end of each reporting period.

Our research and development expenses in 2022 were primarily related to our Phase 3 study in early PD patients. Our research and development expenses in 2021 were primarily related to the AD/PD Trials which began treating patients in August 2020. We expect that our research and development expenses in 2023 and for the next several years will be significantly higher than in 2022 as a result of costs associated with our planned Phase 3 trials. These expenditures are subject to numerous uncertainties regarding timing and cost to completion. Completion of our clinical development and clinical trials may take several years or more and the length of time generally varies according to the type, complexity, novelty and intended use of our product candidates. The cost of clinical trials may vary significantly over the life of a project as a result of differences arising during clinical development, including, among others:

- the number of sites included in the clinical trials;

- the length of time required to enroll suitable patients;
- the size of patient populations participating in the clinical trials;
- the duration of patient follow-ups;
- the development stage of the product candidates; and
- the efficacy and safety profile of the product candidates.

Due to the stage of our research and development, we are unable to accurately determine the duration or completion costs of our development of Buntanetap. As a result of the difficulties of forecasting research and development costs of Buntanetap as well as the other uncertainties discussed above, we are unable to determine when and to what extent we will generate revenues from the commercialization and sale of approved product candidates.

### ***General and Administrative Expenses***

General and administrative expenses consist primarily of salaries, benefits and other related costs, including stock-based compensation, for personnel serving in our executive, finance, accounting, and administrative functions. Our general and administrative expenses also include professional fees for legal services, including patent-related expenses, consulting, tax and accounting services, insurance, rent and general corporate expenses. We expect that our general and administrative expenses will increase with the continued development and potential commercialization of our product candidates. We expect that our general and administrative expenses in 2023 and for the next several years will be significantly higher than in 2022 as we increase our employee count.

### ***Grant Income***

Grants received are recognized as grant income in the statements of operations as and when they are earned for the specific research and development projects for which these grants are designated. Grants payments received in excess of grant income earned are recognized as deferred grant on the balance sheet and grant income earned in excess of grant payments received is recognized as grant receivable on the balance sheets.

### ***Income Taxes***

As of December 31, 2022, the Company had U.S. federal net operating loss (“NOL”) carryforwards of \$27,536,031 which may be available to offset future income tax liabilities. Federal NOL carryforwards generated in 2017 and prior of \$2,764,240 will expire beginning 2032. The remaining federal NOL carryforwards generated beginning in 2018, do not expire. NOL carryforwards generated beginning in 2021 are permitted to offset 80% of taxable income in future years. As of December 31, 2022, the Company also had U. S. state NOL carryforwards of \$30,082,914 which may be available to offset future income tax liabilities and will expire beginning in 2028.

NOL and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service (the “IRS”) and may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant shareholders over a three-year period in excess of 50% as defined under Sections 382 and 383 in the Internal Revenue Code. This could substantially limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on our value immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years.

### ***Critical Accounting Policies and Use of Estimates***

We have based our management’s discussion and analysis of financial condition and results of operations on our financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States of America. The preparation of these financial statements requires us to make estimates that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements as well as the reported revenues and expenses

during the reporting periods. On an ongoing basis, we evaluate our estimates and judgments, including those related to clinical development expenses and stock-based compensation. The clinical development cost to advance any of our product candidates to marketing approval is substantial and involves numerous risks and uncertainties associated with pharmaceutical product development. As a result, we are unable to accurately predict the timing or amount of increased expenses and, as a result, clinical development expense could be materially different as the costs are incurred. We measure and record compensation expense using the applicable accounting guidance for share-based payments using the Black-Scholes option pricing model to value option awards which requires the use of subjective assumptions, including the expected life of the option and expected share price volatility. These assumptions used in calculating the fair value of stock-based awards represent our best estimates and involve inherent uncertainties and the application of judgment. As a result, if factors change and we used different assumptions, stock-based compensation expense could be materially different for stock-based awards.

While our significant accounting policies are more fully discussed in Note 2 to our audited financial statements appearing at the end of this Annual Report on Form 10-K, we believe that the following accounting policies are critical to the process of making significant judgments and estimates in the preparation of our financial statements.

### ***Research and Development Expenses***

We rely on third parties to conduct our clinical studies and to provide services, including data management, statistical analysis and electronic compilation. At the end of each reporting period, we compare the payments made to each service provider to the estimated progress towards completion of the related project. Factors that we consider in preparing these estimates include the number of patients enrolled in studies, milestones achieved and other criteria related to the efforts of our vendors. These estimates are subject to change as additional information becomes available. Depending on the timing of payments to vendors and estimated services provided, we record net prepaid or accrued expenses related to these costs.

### ***Stock-Based Compensation***

We account for grants of stock options to employees and non-employees based on their grant date fair value and recognize compensation expense over the vesting periods. We estimate the fair value of stock options as of the date of grant using the Black-Scholes option pricing model. The Black-Scholes model requires us to make assumptions and judgments about the variables used in the calculations, including the expected term, the expected volatility of our common stock, the risk-free interest rate and the expected dividend rate. Given the lack of a public market for our common stock prior to the IPO, the expected stock price volatility is based on a weighted approach that incorporates the historic daily volatility of our common stock since the IPO and the historic daily volatility of similar companies that have been publicly traded for a period commensurate with the expected term of the option.

## **Results of Operations**

### ***Years ended December 31, 2022 and 2021***

Operating expenses and other income were comprised of the following:

	Year Ended December 31,	
	2022	2021
	(in thousands)	
Operating expenses:		
Research and development .....	\$ 16,515.5	\$ 8,479.0
General and administrative .....	\$ 8,995.7	\$ 6,058.2
Other income:		
Interest income .....	\$ 182.7	\$ 13.3
Grant income .....	\$ —	\$ 36.8

### ***Research and Development Expenses***

Research and development expenses increased by \$8,036.5 thousand for the year ended December 31, 2022 compared to the year ended December 31, 2021. The increase was primarily the result of an increase of \$6,629.5 thousand in expenses related to

our clinical trials, including production of material, an increase in stock-based compensation expense of \$1,357.7 thousand, and an increase of \$202.4 thousand in other personnel expenses, partially offset by a decrease of \$100.5 thousand in expenses related to our long-term toxicology studies.

### ***General and Administrative Expenses***

General and administrative expenses increased by \$2,937.5 thousand for the year ended December 31, 2022 compared to the year ended December 31, 2021. The increase was primarily the result of increases of \$3,097.2 thousand in stock-based compensation expense, partially offset by a decrease of \$230.4 thousand in conference and meeting expenses.

### ***Interest Income, Net***

Interest income, net increased \$159.8 thousand for the year ended December 31, 2022 compared to the year ended December 31, 2021. The increase was primarily the result of higher interest rates compared to the prior year.

### ***Grant Income***

Grant income decreased \$36.8 thousand for the year ended December 31, 2022 compared to the year ended December 31, 2021. The decrease was the result of income recognized related to a grant from the NIH to reimburse the costs of our long-term toxicology studies in rats and dogs, which studies began in November 2019 and were substantially completed as of December 31, 2020.

### ***Liquidity and Capital Resources***

Since our inception in 2008, we have devoted most of our cash resources to research and development and general and administrative activities. We have financed our operations primarily with the proceeds from the sale of common stock, convertible preferred stock and convertible promissory notes. To date, we have not generated any revenues from the sale of products, and we do not anticipate generating any revenues from the sales of products for the foreseeable future. We have incurred losses and generated negative cash flows from operations since inception. As of December 31, 2022, our principal source of liquidity was our cash and cash equivalents, which totaled \$28,377.7 thousand.

### ***Equity Financings***

We closed an equity offering on May 26, 2021, raising gross proceeds of \$50,000.0 thousand and net proceeds of \$46,648.4 thousand, after deducting underwriting discounts and issuance costs.

### ***Future Capital Requirements***

We do not have sufficient capital on hand to fund our operations for the next 12 months and will need to raise additional capital to meet our obligations as they become due. We believe that our current cash and cash equivalents and funding from existing grants will be sufficient to fund our operating expenses and capital expenditure requirements until the fourth quarter of 2023, including our ongoing Phase 2/3 AD Trial and our ongoing Phase 3 PD Trial. We will need to raise substantial additional capital to complete the development and commercialization of our product candidates through public or private equity offerings, debt financings, collaboration and licensing arrangements or other financing alternatives. However, there can be no assurance that we will be successful in raising additional capital or that such capital, if available, will be on terms that are acceptable to us. We have no committed external sources of funds. If we are unable to raise sufficient additional capital or defer sufficient operating expenses, we may be compelled to reduce the scope of our operations.

We expect to incur significant operating losses for the foreseeable future, and for these losses to further increase, as we ramp up our clinical development programs and begin activities for commercial launch readiness. We may also encounter unforeseen expenses, difficulties, complications, delays and other currently unknown factors that could adversely affect our business.

Our future funding requirements, both near and long-term, will depend on many factors, including, but not limited to:

- the initiation, progress, timing, costs and results of preclinical studies and clinical trials, including patient enrollment in such trials, for Buntanetap or any other future product candidates;
- the clinical development plans we establish for Buntanetap and any other future product candidates, including any modifications to clinical development plans based on feedback that we may receive from regulatory authorities;
- the number and characteristics of product candidates that we discover or in-license and develop;
- the outcome, timing and cost of regulatory meetings and reviews by the FDA and comparable foreign regulatory authorities, including the potential for the FDA or comparable foreign regulatory authorities to require that we perform more studies than those that we currently expect;
- the requirements of regulatory authorities in any additional jurisdictions in which we may seek approval for Buntanetap and any future product candidates and our anticipated timing for seeking approval in such jurisdictions;
- the costs of filing, prosecuting, defending and enforcing any patent claims and maintaining and enforcing other intellectual property and proprietary rights;
- the effects of competing technological and market developments;
- the costs associated with hiring additional personnel and consultants as our business grows, including additional executive officers and clinical development, regulatory, CMC quality and commercial personnel;
- the costs and timing of the implementation of commercial-scale manufacturing activities, if any product candidate is approved, including as a result of inflation, any supply chain issues or component shortages;
- the costs and timing of establishing sales, marketing and distribution capabilities for any product candidates for which we may receive regulatory approval;
- our ability to achieve sufficient market acceptance, coverage and adequate reimbursement from third-party payors and adequate market share and revenue for any approved products;
- the terms and timing of establishing and maintaining collaborations, licenses and other similar arrangements;
- the costs associated with any products or technologies that we may in-license or acquire; and
- any delays and cost increases that may result from the COVID-19 or any future pandemic.

A change in the outcome of any of these or other variables with respect to the development of any of our product candidates could significantly change the costs and timing associated with the development of that product candidate. Furthermore, our operating plans may change in the future, and we will continue to require additional capital to meet operational needs and capital requirements associated with such operating plans. If we raise additional funds by issuing equity securities, our stockholders may experience dilution. Any future debt financing into which we enter may impose upon us additional covenants that restrict our operations, including limitations on our ability to incur liens or additional debt, pay dividends, repurchase our common stock, make certain investments or engage in certain merger, consolidation or asset sale transactions. Any debt financing or additional equity that we raise may contain terms that are not favorable to us or our stockholders.

Adequate funding may not be available to us on acceptable terms or at all. Our potential inability to raise capital when needed could have a negative impact on our financial condition and our ability to pursue our business strategies. If we are unable to raise additional funds as required, we may need to delay, reduce, or terminate some or all development programs and clinical trials. We may also be required to sell or license our rights to product candidates in certain territories or indications that we would otherwise prefer to develop and commercialize ourselves. If we are required to enter into collaborations and other arrangements to address our liquidity needs, we may have to give up certain rights that limit our ability to develop and commercialize our product candidates or



may have other terms that are not favorable to us or our stockholders, which could materially and adversely affect our business and financial prospects. See the section of this Annual Report on Form 10-K titled “Risk Factors” for additional risks associated with our substantial capital requirements.

### ***Cash Flows***

The following table summarizes our cash flows from operating, investing and financing activities.

	Year Ended December 31,	
	2022	2021
	(in thousands)	
<b>Statement of Cash Flows Data:</b>		
Total net cash (used in) provided by:		
Operating activities.....	\$ (17,312.9)	\$ (9,132.1)
Financing activities.....	4.6	46,743.5
Net (decrease) increase in cash and cash equivalents .....	\$ (17,308.3)	\$ 37,611.4

### ***Operating Activities***

For the year ended December 31, 2022, cash used in operations was \$17,312.9 thousand compared to \$9,132.1 thousand for the year ended December 31, 2021. The increase in cash used in operations was primarily the result of the costs associated with our AD/PD Trials and higher personnel expenses.

We expect cash used in operating activities to increase in 2023 as compared to 2022 due to an expected increase in our operating losses associated with ongoing development of our product candidates and planned increases in our personnel count.

### ***Financing Activities***

Cash provided by financing activities was \$4.6 thousand during the year ended December 31, 2022, attributable to proceeds from the exercise of stock options.

Cash provided by financing activities was \$46,743.5 thousand during the year ended December 31, 2021, attributable to net proceeds from our equity offering of approximately \$46,648.4 thousand, and proceeds from the exercise of stock options of \$95.1 thousand.

### **Restatement of Previously Issued Quarterly Financial Statements**

During its preparation of its 2022 audited combined financial statements and notes thereto, the Company concluded that there were material research and development expenses and related balance sheet errors in its previously issued unaudited condensed financial statements as of and for each of the quarterly and year to date periods ended March 31, 2022, June 30, 2022 and September 30, 2022, primarily relating to the timing of payments for research and development expenses and recognition of expenses.

The Company noted the following items were improperly expensed during the three months ended March 31, 2022:

- Payments, in the amount of \$800,840, were improperly recorded in research and development expenses during the three months ended March 31, 2022. These amounts should have been recorded as prepaid expenses and other current assets as of March 31, 2022.
- Research and development expense amounts totaling \$140,690 were not recorded during the three months ended March 31, 2022. This amount should have been recorded in accrued expenses and other current liabilities as of March 31, 2022.

These errors in the accounting for research and development expenses resulted in an understatement of prepaid assets and other current assets of \$800,840, accrued expenses and other current liabilities of \$140,690 and an overstatement of operating expenses and net loss of \$660,150 as of and for the three months ended March 31, 2022.

The Company noted the following items were improperly expensed during the three and six months ended June 30, 2022:

- Payments, in the amount of \$2,883,977 were improperly recorded in research and development expenses during the three months ended June 30, 2022. These amounts should have been recorded in prepaid expenses and other current assets as of June 30, 2022. Additionally, \$102,232 was expensed during the three months ended June 30, 2022 related to the prior quarter restatements.

These errors, including the errors from the three months ended March 31, 2022, in the accounting for research and development expenses resulted in a cumulative understatement of prepaid assets and other current assets of \$3,441,895, as of June 30, 2022, and an overstatement operating expenses and net loss of \$2,781,745 and \$3,441,895 for the three and six months ended June 30, 2022, respectively.

The Company noted the following items were improperly expensed during the three and nine months ended September 30, 2022:

- Payments, in the amount of \$1,320,321, were improperly recorded in research and development expenses during the three months ended September 30, 2022. These amounts should have been recorded in prepaid expenses and other current assets as of September 30, 2022. Additionally, \$130,826 was expensed during the three months ended September 30, 2022 related to the prior quarter restatements.

These errors, including the errors from the six months ended June 30, 2022, in the accounting for research and development expenses resulted in an understatement of prepaid assets and other current assets of \$4,631,390 as of September 30, 2022, and an overstatement of operating expenses and net loss of \$1,189,495 and \$4,631,390 for the three and nine months ended September 30, 2022, respectively.

Detailed restatements of the Company's condensed quarterly financial statements are provided in this Annual Report on Form 10-K, Note 12 - *Restatement of Previously Issued Unaudited Condensed Financial Statements*.

## **Recent Accounting Pronouncements**

In November 2021, the FASB issued ASU No. 2021-10, Government Assistance (Topic 832): Disclosures by Business Entities about Government Assistance. The amendments in ASU 2021-10 require annual disclosures about transactions with a government that are accounted for by applying a grant or contribution accounting model by analogy. The new disclosure requirements include information about the nature of the transactions and the related accounting policy used to account for the transactions; the line items on the balance sheet and income statement that are affected by the transactions, and the amounts applicable to each financial statement line item; and significant terms and conditions of the transactions, including commitments and contingencies. The guidance is effective for fiscal years beginning after December 15, 2021, with early adoption permitted, and may be adopted prospectively or retrospectively. We adopted this standard prospectively. As such, the adoption did not have an impact on our financial statements.

## **JOBS Act**

Section 107 of the JOBS Act also provides that an “emerging growth company” can take advantage of the extended transition period provided in Section 7(a)(2)(B) of the Securities Act for complying with new or revised accounting standards. In other words, an “emerging growth company” can delay the adoption of new or revised accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

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

This item is not required for smaller reporting companies.

## **Item 8. Financial Statements and Supplementary Data.**

Our financial statements, accompanying notes and Report of Independent Registered Public Accounting Firm are included in this Annual Report on Form 10-K beginning on page F-1, which are incorporated in this Item 8 by reference.

## **Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure.**

None.

## **Item 9A. Controls and Procedures.**

### **Evaluation of Disclosure Controls and Procedures.**

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, has evaluated the effectiveness of our disclosure controls and procedures (as such term is defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act) as of the end of the period covered by this Annual Report on Form 10-K. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost benefit relationship of possible controls and procedures. Based on such evaluation, our Chief Executive Officer and Chief Financial Officer have concluded that, as of the end of the period covered by this report, as a result of the material weaknesses in our internal control, our disclosure controls and procedures were not effective to ensure that the information required to be disclosed by us in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in SEC rules and forms, and that information required to be disclosed in the reports we file or submit under the Exchange Act is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as our principal financial and accounting officer, to allow timely decisions regarding required disclosures.

### **Identified Material Weakness**

In connection with the audit of our financial statements as of December 31, 2022 and 2021 and for the years ended December 31, 2022 and 2021, we identified a material weakness in our internal control over financial reporting. A material weakness is a deficiency, or a combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of our annual or interim financial statements will not be prevented or detected on a timely basis. The material weakness related to the proper classification of research and development expenses, which impacted our previously issued condensed financial statements as of and for the three months ended March 31, 2022, three and six months ended June 30, 2022 and three and nine months ended September 30, 2022.

### **Remediation Plan**

Our management, with the oversight of the Audit Committee of the Board of Directors, has updated our internal processes and controls to strengthen their effectiveness and developed a remediation plan which includes the following actions:

- Enhance our review procedures over significant contracts with contract manufacturing organizations and contract research organizations;
- Augment existing staff; and
- Strengthen the review process.

We will not be able to conclude whether the actions we are taking will fully remediate the material weakness in our internal control over financial reporting until the updated controls have operated for a sufficient period of time and management has

concluded, through testing, that such controls are operating effectively. We may also conclude that additional measures may be required to remediate the material weakness in our internal control over financial reporting, which may necessitate further action.

### **Management's Report on Internal Control Over Financial Reporting**

Management is responsible for establishing and maintaining adequate internal control over financial reporting as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act. Our internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Management utilized the criteria established in the Internal Control – Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) to assess the effectiveness of our internal control over financial reporting as of December 31, 2022. Based on the assessment, management has concluded that, as of December 31, 2022, our internal control over financial reporting was not effective, due to the remaining material weakness in our internal control over financial reporting described above.

As an emerging growth company, management's assessment of internal control over financial reporting was not subject to attestation by our independent registered public accounting firm.

### **Changes in Internal Control Over Financial Reporting**

There was no change in our internal control over financial reporting identified in connection with the evaluation required by Rule 13a-15(d) and 15d-15(d) of the Exchange Act that occurred during the quarter ended December 31, 2022 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting, as the material weakness relating to our internal control over financial reporting described above was identified subsequent to December 31, 2022. We are now taking actions to remediate the material weakness, which may result in changes in our internal control over financial reporting in periods subsequent to December 31, 2022.

### **Item 9B. Other Information.**

None.

## **PART III**

### **Item 10. Directors and Executive Officers and Corporate Governance.**

We incorporate the information required by this Item 10 by reference to the definitive proxy statement for our 2023 annual meeting of shareholders, to be filed with the SEC.

The following is a list of our executive officers as of the date of this Annual Report.

<u>Name</u>	<u>Position</u>
Maria Maccicchini	President and Chief Executive Officer
Henry Hagopian	Chief Financial Officer

### **Item 11. Executive Compensation.**

We incorporate the information required by this Item 11 by reference to the definitive proxy statement for our 2023 annual meeting of shareholders, to be filed with the SEC.

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

We incorporate the information required by this Item 12 by reference to the definitive proxy statement for our 2023 annual meeting of shareholders, to be filed with the SEC.

**Equity Compensation Plan Information**

Plan category	Number of securities to be issued upon exercise of outstanding options, warrants and rights	Weighted-average exercise price of outstanding options, warrants and rights	Number of securities remaining available for future issuance under equity compensation plans (excluding securities reflected in column (a))
	(a)	(b)	(c)
Equity compensation plans approved by security holders . . . . .	1,657,342	\$ 13.95	392,874
Equity compensation plans not approved by security holders . . . . .	2,400	\$ 7.50	—
Total . . . . .	1,659,742	\$ 13.95	392,874

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

We incorporate the information required by this Item 13 by reference to the definitive proxy statement for our 2023 annual meeting of shareholders, to be filed with the SEC.

**Item 14. Principal Accountants Fees and Services.**

We incorporate the information required by this Item 14 by reference to the definitive proxy statement for our 2023 annual meeting of shareholders, to be filed with the SEC.

**PART IV****Item 15. Exhibits and Financial Statement Schedules.**

## (a) Documents filed as part of this report:

1. Financial Statements. The financial statements as set forth under Item 8 of this Annual Report on Form 10-K are incorporated herein.
2. Financial Statement Schedules. All financial statement schedules have been omitted because they are not applicable, not required, or the information is shown in the financial statements or related notes.
3. Exhibits. See (b) below.

## (b) Exhibits

Exhibit Number	Description of Exhibit
3.1	Amended and Restated Certificate of Incorporation of the Registrant. (Incorporated by reference to Exhibit 3.1 to Form 8-K filed February 6, 2020.)
3.2	Amended and Restated Bylaws of the Registrant. (Incorporated by reference to Exhibit 3.2 to Form 8-K filed February 6, 2020.)

Exhibit Number	Description of Exhibit
4.1	Specimen Certificate evidencing shares of the Registrant's common stock. (Incorporated by reference to Exhibit 4.1 to Amendment No. 3 to Form S-1 filed September 20, 2019.)
4.2	Form of Warrant to purchase common stock issued to ThinkEquity, a division of Fordham Financial Management, Inc. in connection with the closing of the IPO. (Incorporated by reference to Exhibit 4.2 to Form 10-K filed March 25, 2020.)
4.3	Description of Registrant's Securities. (Incorporated by reference to Exhibit 4.3 to Form 10-K filed March 25, 2020.)
10.1+	Second Amended and Restated Employment Agreement dated as of March 24, 2020 between the Registrant and Maria Maccecchini. (Incorporated by reference to Exhibit 10.1 to Form 10-K filed March 25, 2020.)
10.2+	Annovis Bio, Inc. 2018 Equity Incentive Plan. (Incorporated by reference to Exhibit 10.2 to Form S-1 filed July 3, 2019.)
10.3	Registration Rights Agreement dated as of December 19, 2014 among the Registrant and the signatories thereto. (Incorporated by reference to Exhibit 10.5 to Amendment No. 1 to Form S-1 filed August 8, 2019.)
10.4	Investigator-Initiated Clinical Trial Agreement dated June 27, 2016 between The Regents of the University of California and the Registrant. (Incorporated by reference to Exhibit 10.7 to Form S-1 filed July 3, 2019.)
10.5+	Annovis Bio, Inc. 2019 Equity Incentive Plan. (Incorporated by reference to Appendix A to the Proxy Statement on Schedule 14A filed on April 19, 2021.)
10.6+	Form of Stock Option Award Agreement for the Annovis Bio, Inc. 2019 Equity Incentive Plan.
10.7+	Offer Letter, dated August 29, 2022, by and between the Registrant and Henry Hagopian III. (Incorporated by reference to Exhibit 10.1 to Current Report on Form 8-K filed August 29, 2022.)
10.8+	Separation Agreement, dated September 9, 2022, by and between the Registrant and Jeffrey B. McGroarty. (Incorporated by reference to Exhibit 10.1 to Current Report on Form 8-K filed September 12, 2022.)
23.1	Consent of WithumSmith+Brown, PC.
24.1	Power of Attorney. (Included on signature page to this Annual Report on Form 10-K.)
31.1	Certification Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1	Certification Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
32.2	Certification Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101.INS	XBRL Instance Document – the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document.
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Extension Labels Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document

104                      Cover Page Interactive Data File – the cover page interactive data file does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document.

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+     Indicates management contract or compensatory plan.

(c) Financial Statement Schedules

None.

**Item 16. Form 10-K Summary.**

None.

**ANNOVIS BIO, INC.**  
**Table of Contents**

	<b><u>Page(s)</u></b>
Report of Independent Registered Public Accounting Firm .....	F-2
Balance Sheets as of December 31, 2022 and 2021 .....	F-3
Statements of Operations for the Years ended December 31, 2022 and 2021 .....	F-4
Statements of Changes in Stockholders' Equity for the Years ended December 31, 2022 and 2021 .....	F-5
Statements of Cash Flows for the Years ended December 31, 2022 and 2021 .....	F-6
Notes to Financial Statements .....	F-7



## **REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM**

To the Stockholders and the Board of Directors of Annovis Bio, Inc.

### **Opinion on the Financial Statements**

We have audited the accompanying balance sheets of Annovis Bio, Inc. (the “Company”), as of December 31, 2022 and 2021, and the related statements of operations, changes in stockholders’ equity and cash flows for each of the two years in the period ended December 31, 2022 and the related notes (collectively referred to as the “financial statements”). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2022 and 2021, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2022, in conformity with accounting principles generally accepted in the United States of America.

### **Substantial Doubt Regarding Going Concern**

The accompanying financial statements have been prepared assuming that the entity will continue as a going concern. As discussed in Note 1 to the financial statements, the entity has a history of recurring losses and negative cash flows from operations that raise substantial doubt about its ability to continue as a going concern. Management's plans in regard to these matters are also described in Note 1. The financial statements do not include any adjustments that might result from the outcome of this uncertainty. Our opinion is not modified with respect to this matter.

### **Restatement of Previously Issued Financial Statements**

As discussed in Note 12 to the financial statements, the Company has restated its 2022 quarterly financial information for an error in the accounting for research and development costs.

### **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 audits to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company’s internal control over financial reporting. Accordingly, we express no such opinion.

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

/s/ WithumSmith+Brown, PC

We have served as the Company’s auditor since 2019.

East Brunswick, New Jersey  
March 31, 2023

PCAOB ID Number 100

# **ANNOVIS BIO, INC.**

## **Balance Sheets**

	<b>As of December 31,</b>	
	<b>2022</b>	<b>2021</b>
<b>Assets</b>		
Current assets:		
Cash and cash equivalents .....	\$ 28,377,693	\$ 45,686,014
Prepaid expenses and other current assets .....	7,644,376	315,464
Total current assets .....	<u>36,022,069</u>	<u>46,001,478</u>
Total assets .....	<u>\$ 36,022,069</u>	<u>\$ 46,001,478</u>
<b>Liabilities and Stockholders' Equity</b>		
Current liabilities:		
Accounts payable .....	\$ 3,961,254	\$ 688,074
Accrued expenses .....	3,737,285	818,440
Total current liabilities .....	<u>7,698,539</u>	<u>1,506,514</u>
Total liabilities .....	<u>7,698,539</u>	<u>1,506,514</u>
Commitments and contingencies (Note 7)		
Stockholders' equity:		
Preferred stock - \$0.0001 par value, 2,000,000 shares authorized and 0 shares issued and outstanding .....	—	—
Common stock - \$0.0001 par value, 35,000,000 shares authorized and 8,163,923 and 8,100,570 shares issued and outstanding at December 31, 2022 and December 31, 2021, respectively .....	816	810
Additional paid-in capital .....	82,377,488	73,220,361
Accumulated deficit .....	<u>(54,054,774)</u>	<u>(28,726,207)</u>
Total stockholders' equity .....	<u>28,323,530</u>	<u>44,494,964</u>
Total liabilities and stockholders' equity .....	<u>\$ 36,022,069</u>	<u>\$ 46,001,478</u>

See accompanying notes to financial statements.

# ANNOVIS BIO, INC.

## Statements of Operations

	Year Ended December 31,	
	2022	2021
Operating expenses:		
Research and development .....	\$ 16,515,543	\$ 8,479,031
General and administrative .....	8,995,736	6,058,190
Total operating expenses .....	<u>25,511,279</u>	<u>14,537,221</u>
Operating loss .....	(25,511,279)	(14,537,221)
Other income:		
Interest income .....	182,712	13,335
Grant income .....	—	36,754
Total other income .....	<u>182,712</u>	<u>50,089</u>
Loss before income taxes .....	(25,328,567)	(14,487,132)
Income tax expense (benefit) .....	—	—
Net loss .....	<u>\$ (25,328,567)</u>	<u>\$ (14,487,132)</u>
Basic and diluted loss per common share .....	<u>\$ (3.10)</u>	<u>\$ (1.90)</u>
Weighted average number of common shares outstanding, basic and diluted .....	<u>8,162,326</u>	<u>7,626,278</u>

See accompanying notes to financial statements.

**ANNOVIS BIO, INC.**

**Statements of Changes in Stockholders' Equity  
For the Years Ended December 31, 2022 and 2021**

	<b>Stockholders' Equity (Deficit)</b>				
	<b>Common Stock</b>		<b>Additional</b>	<b>Total</b>	<b>Total</b>
	<b>Shares</b>	<b>Amount</b>	<b>Paid-In Capital</b>	<b>Accumulated Deficit</b>	<b>Stockholders' Equity</b>
Balance, December 31, 2020 . . . . .	6,891,608	\$ 689	\$ 21,779,340	\$ (14,239,075)	\$ 7,540,954
Issuance of common stock, net of issuance costs . . . . .	1,000,000	100	46,648,313	—	46,648,413
Exercise of stock options . . . . .	155,038	16	95,086	—	95,102
Cashless exercise of warrants . . . . .	53,924	5	(5)	—	—
Stock-based compensation expense . . . . .	—	—	4,697,627	—	4,697,627
Net loss . . . . .	—	—	—	(14,487,132)	(14,487,132)
Balance, December 31, 2021 . . . . .	8,100,570	810	73,220,361	(28,726,207)	44,494,964
Exercise of stock options . . . . .	63,353	6	4,607	—	4,613
Stock-based compensation expense . . . . .	—	—	9,152,520	—	9,152,520
Net loss . . . . .	—	—	—	(25,328,567)	(25,328,567)
Balance, December 31, 2022 . . . . .	<u>8,163,923</u>	<u>\$ 816</u>	<u>\$ 82,377,488</u>	<u>\$ (54,054,774)</u>	<u>\$ 28,323,530</u>

See accompanying notes to financial statements.

# **ANNOVIS BIO, INC.**

## **Statements of Cash Flows**

	<b>Year Ended December 31,</b>	
	<b>2022</b>	<b>2021</b>
Cash flows from operating activities:		
Net loss .....	\$ (25,328,567)	\$ (14,487,132)
Adjustments to reconcile net loss to net cash used in operating activities:		
Stock-based compensation expense .....	9,152,520	4,697,627
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets .....	(7,328,912)	(270,788)
Accounts payable .....	3,273,180	346,218
Accrued expenses .....	2,918,845	581,916
Net cash used in operating activities .....	<u>(17,312,934)</u>	<u>(9,132,159)</u>
Cash flows from financing activities:		
Proceeds from issuance of common stock, net of issuance costs .....	—	46,648,413
Proceeds from exercise of stock options .....	4,613	95,102
Net cash provided by financing activities .....	<u>4,613</u>	<u>46,743,515</u>
Net (decrease) increase in cash and cash equivalents .....	(17,308,321)	37,611,356
Cash and cash equivalents, beginning of year .....	45,686,014	8,074,658
Cash and cash equivalents, end of year .....	<u>\$ 28,377,693</u>	<u>\$ 45,686,014</u>

See accompanying notes to financial statements.

**Annovis Bio, Inc.**  
**Notes to Financial Statements**

**December 31, 2022 and 2021**

**(1) Nature of Business, Going Concern and Management's Plans**

Annovis Bio, Inc. (the "Company" or "Annovis") was incorporated on April 29, 2008, under the laws of the State of Delaware. Annovis is a clinical-stage drug platform company addressing neurodegeneration such as Alzheimer's disease ("AD") and Parkinson's disease ("PD"). The toxic cascade in neurodegeneration begins with high levels of neurotoxic proteins which lead to impaired axonal transport, inflammation, death of nerve cells and loss of cognition and motor function. The Company's lead product candidate, Buntanetap, is a small molecule administered orally that is designed to attack neurodegeneration by entering the brain and inhibiting the translation of multiple neurotoxic proteins thereby impeding the toxic cascade.

Since its founding, the Company has been engaged in organizational activities, including raising capital, and research and development activities. The Company has not generated substantial revenues and has not yet achieved profitable operations, nor has it ever generated positive cash flows from operations. There is no assurance that profitable operations, if achieved, could be sustained on a continuing basis. The Company is subject to those risks associated with any clinical stage pharmaceutical company that has substantial expenditures for research and development. There can be no assurance that the Company's research and development projects will be successful, that products developed will obtain necessary regulatory approval, or that any approved product will be commercially viable. In addition, the Company operates in an environment of rapid technological change and is largely dependent on the services of its employees and consultants. Further, the Company's future operations are dependent on the success of the Company's efforts to raise additional capital.

The Company has a history of incurring net losses and anticipates incurring additional losses until such time, if ever, that it can generate significant revenue from its product candidates currently in development. The Company's primary source of capital has been the issuance of equity securities.

On May 26, 2021, the Company closed an underwritten public offering of 1,000,000 shares of its common stock at an offering price of \$50.00 per share, for gross proceeds of \$50.0 million. The net proceeds of the offering were approximately \$46.6 million, after deducting underwriting discounts and issuance costs paid by the Company. The Company's common stock trades on the New York Stock Exchange under the ticker symbol "ANVS".

Since the Company's inception, the Company has incurred losses and negative cash flows from operations. At December 31, 2022, the Company had an accumulated deficit of \$54.1 million. The Company's net loss was \$25.3 million and \$14.5 million for the years ended December 31, 2022 and 2021, respectively. The Company follows the provisions of Financial Accounting Standards Board, or FASB, Accounting Standards Codification, or ASC, Topic 205-40, Presentation of Financial Statements-Going Concern, or ASC 205-40, which requires management to assess the Company's ability to continue as a going concern for one year after the date the financial statements are issued. The Company expects that its existing balance of cash and cash equivalents as of December 31, 2022 is sufficient to fund operations through the third quarter of 2023, but not for more than one year after the date of this filing and therefore management has concluded that substantial doubt exists about the Company's ability to continue as a going concern. Management's plans to mitigate this risk include raising additional capital through equity. Management's plans may also include the deferral of certain operating expenses unless and until additional capital is received. However, there can be no assurance that the Company will be successful in raising additional capital or that such capital, if available, will be on terms that are acceptable to the Company, or that the Company will be successful in deferring certain operating expenses. If the Company is unable to raise sufficient additional capital or defer sufficient operating expenses, the Company may be compelled to reduce the scope of its operations.

**(2) Summary of Significant Accounting Policies**

***(a) Basis of Presentation***

The accompanying financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("U.S. GAAP"). Any reference in these notes to applicable guidance is meant to refer to U.S. GAAP as

found in the Accounting Standards Codification (“ASC”) and Accounting Standards Update (“ASU”) of the Financial Accounting Standards Board (“FASB”).

***(b) Use of Estimates***

The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, including disclosure of contingent assets and liabilities, at the date of the financial statements, and the reported amounts of revenues and expenses during the reporting period. Due to the uncertainty of factors surrounding the estimates or judgments used in the preparation of the financial statements, actual results may materially vary from these estimates.

Significant items subject to such estimates and assumptions include progress towards completion of research and development projects, stock-based compensation expense, grant income and contingent liabilities. Future events and their effects cannot be predicted with certainty; accordingly, accounting estimates require the exercise of judgment. Accounting estimates used in the preparation of these financial statements change as new events occur, as more experience is acquired, as additional information is obtained and as the operating environment changes.

***(c) Basic and Diluted Net Income per Share***

Basic net loss per share is determined using the weighted average number of shares of common stock outstanding during each period. Diluted net loss per share includes the effect, if any, from the potential exercise or conversion of securities, such as stock options and warrants, which would result in the issuance of incremental shares of common stock. The computation of diluted net loss per share does not include the conversion of securities that would have an anti-dilutive effect.

***(d) Cash and Cash Equivalents***

The Company considers all highly liquid investments with original maturities of three months or less to be cash equivalents. The Company has significant cash balances at financial institutions which throughout the year regularly exceed the federally insured limit of \$250,000. Any loss incurred or a lack of access to such funds could have a significant adverse effect on the Company’s financial condition, results of operations, and cash flows.

***(e) Issuance Costs Associated with Equity Issuances***

Issuance costs incurred in connection with the Company’s equity issuances, which primarily consisted of direct incremental legal, printing, listing and accounting fees, are offset against proceeds received in the issuances and charged to additional paid-in capital in the period the equity issuance is completed.

***(f) Fair Value of Financial Instruments***

The Company’s financial instruments include cash and cash equivalents, accounts payable and accrued expenses. Cash and cash equivalents are reported at fair value. The recorded carrying amount of accounts payable and accrued expenses reflect their fair value due to their short-term nature.

***(g) Research and Development***

Research and development costs are either expensed as incurred or recorded separately as a prepaid asset, and the expense recognized when the service is performed and are primarily comprised of personnel-related expenses and external research and development expenses incurred under arrangements with third parties, such as contract research organizations and consultants. At the end of each reporting period, the Company compares the payments made to each service provider to the estimated progress towards completion of the related project. Factors that the Company considers in preparing these estimates include the number of patients enrolled in studies, milestones achieved, and other criteria related to the efforts of its vendors. These estimates will be subject to change as additional information becomes available. Depending on the timing of payments to vendors and estimated services provided, the Company will record net prepaid or accrued expenses related to these costs. Prepaid clinical expenses represent valid future economic benefits based on our contracts with our vendors, and are realized in the ordinary course of business.

#### ***(h) Grant Income***

Grants received are recognized as grant income in the statements of operations as and when they are earned for the specific research and development projects for which these grants are designated. Grants payments received in excess of grant income earned are recognized as deferred grant on the balance sheet and grant income earned in excess of grant payments received is recognized as grant receivable on the balance sheets.

#### ***(i) Stock-Based Compensation***

Stock-based compensation cost is measured at the grant date based on the fair value of the award and is recognized as expense on a straight-line basis over the requisite service period, which is generally the vesting period. Forfeitures are recognized in compensation expense in the period when they occur. For stock awards that vest based on performance conditions (e.g. achievement of certain milestones), expense is recognized when it is probable that the condition will be met. Stock option modification expense is calculated as the incremental fair value of the modified award over the fair value of the original award measured immediately before the award's terms were modified. For vested awards, the incremental fair value is recognized immediately.

The Company uses the Black-Scholes option pricing model to value its option awards which requires the use of subjective assumptions, including the expected life of the option and expected share price volatility. The assumptions used in calculating the fair value of stock-based awards represent management's best estimates and involve inherent uncertainties and the application of management's judgment. As a result, if factors change and management uses different assumptions, stock-based compensation expense could be materially different for future awards.

Upon exercise of stock options, the Company issues shares first from treasury stock, if available, then from authorized but unissued shares.

#### ***(j) Income Taxes***

The Company provides for income taxes using the asset and liability approach. Deferred tax assets and liabilities are recorded based on the differences between the financial statement and tax bases of assets and liabilities and the tax rates in effect when these differences are expected to reverse. Deferred tax assets are reduced by a valuation allowance if, based on the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized. As of December 31, 2022 and 2021, the Company had a full valuation allowance against its deferred tax assets.

The Company is subject to the provisions of ASC 740, Income Taxes, which prescribes a more likely-than-not threshold for the financial statement recognition of uncertain tax positions. ASC 740 clarifies the accounting for income taxes by prescribing a minimum recognition threshold and measurement attribute for the financial statement recognition and measurement of a tax position taken or expected to be taken in a tax return. There are currently no open federal or state tax audits. The Company has not recorded any liability for uncertain tax positions at December 31, 2022 or 2021.

#### ***(k) Recent Accounting Pronouncements***

In November 2021, the FASB issued ASU No. 2021-10, Government Assistance (Topic 832): Disclosures by Business Entities about Government Assistance. The amendments in ASU 2021-10 require annual disclosures about transactions with a government that are accounted for by applying a grant or contribution accounting model by analogy. The new disclosure requirements include information about the nature of the transactions and the related accounting policy used to account for the transactions; the line items on the balance sheet and income statement that are affected by the transactions, and the amounts applicable to each financial statement line item; and significant terms and conditions of the transactions, including commitments and contingencies. The guidance is effective for fiscal years beginning after December 15, 2021, with early adoption permitted, and may be adopted prospectively or retrospectively. We adopted this standard prospectively. As such, the adoption did not have an impact on our financial statements.

#### ***(3) Fair Value Measurements***

The Company measures certain assets and liabilities at fair value in accordance with ASC 820, Fair Value Measurements and Disclosures. ASC 820 defines fair value as the price that would be received to sell an asset or paid to transfer a liability (the exit price)



in an orderly transaction between market participants at the measurement date. The guidance in ASC 820 outlines a valuation framework and creates a fair value hierarchy that serves to increase the consistency and comparability of fair value measurements and the related disclosures. In determining fair value, the Company maximizes the use of quoted prices and observable inputs. Observable inputs are inputs that market participants would use in pricing the asset or liability based on market data obtained from independent sources. The fair value hierarchy is broken down into three levels based on the source of inputs as follows:

Level 1—Valuations based on unadjusted quoted prices in active markets for identical assets or liabilities.

Level 2—Valuations based on observable inputs and quoted prices in active markets for similar assets and liabilities.

Level 3—Valuations based on unobservable inputs and models that are supported by little or no market activity.

The following tables provides the carrying value and fair value of certain financial assets and liabilities of the Company measured at fair value on a recurring basis as of December 31, 2022 and 2021:

	<u>Carrying Value</u>	<u>Fair Value Measurement at December 31, 2022</u>		
		<u>Level 1</u>	<u>Level 2</u>	<u>Level 3</u>
Cash equivalents. . . . .	\$ 26,001,934	\$ 26,001,934	\$ —	\$ —

	<u>Carrying Value</u>	<u>Fair Value Measurement at December 31, 2021</u>		
		<u>Level 1</u>	<u>Level 2</u>	<u>Level 3</u>
Cash equivalents. . . . .	\$ 60,031	\$ 60,031	\$ —	\$ —

#### (4) Grant Income

In September 2019, as modified in September 2020, the Company received a Notice of Award for a \$1.9 million grant from the National Institute on Aging of the National Institutes of Health (the “NIH”) to cover costs of long-term chronic toxicology studies of Buntanetap in rats and dogs. The Company began the long-term chronic toxicology studies in November 2019. The Company recognized grant income of \$0 and \$36,754 for the years ended December 31, 2022 and 2021, respectively, in connection with the NIH grant. The Company received payments under the grant of \$36,754 during the year ended December 31, 2021 and recorded a grant receivable of \$0 as of December 31, 2021, and had no unreimbursed, eligible costs incurred under the grant. As of December 31, 2022, there were no remaining funds available under the grant.

#### (5) Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consisted of the following:

	<u>As of December 31,</u>	
	<u>2022</u>	<u>2021</u>
Prepaid expenses . . . . .	\$ 67,532	\$ 43,736
Prepaid clinical trial expenses . . . . .	7,528,250	232,752
Prepaid insurance . . . . .	37,356	29,111
Security deposits . . . . .	11,238	9,865
	<u>\$ 7,644,376</u>	<u>\$ 315,464</u>

## **(6) Accrued Expenses**

Accrued expenses consisted of the following:

	<b>As of December 31,</b>	
	<b>2022</b>	<b>2021</b>
Payroll and related benefits . . . . .	\$ 556,827	\$ 712,768
Accrued professional and clinical fees . . . . .	3,180,458	105,672
	<u>\$ 3,737,285</u>	<u>\$ 818,440</u>

See Note 7 for further detail on the accrued license payments.

## **(7) Commitments and Contingencies**

### ***(a) Research & Development***

The Company has entered contracts with contract research organizations (CROs) and contract manufacturers (CMOs) related to the Company's clinical trials. The contracts require upfront payments, milestone payments, and pass through cost reimbursement, to be made. While the contracts are cancellable with (written) notice, the Company is obligated for payments for services rendered through the termination date of the project with the CRO/CMO.

### ***(b) Leases***

The Company leases its office facilities under a month-to-month operating lease. Total rental expense was \$66,802 and \$51,760 for the years ended December 31, 2022 and 2021, respectively.

### ***(c) License Agreement***

The Company previously licensed the rights to certain chemical compounds, know-how and intellectual property rights that may be suitable for the development of human therapeutics from a subsidiary of Horizon Therapeutics, PLC (the "Licensor"). Under the license agreement, the Company paid a minimum annual fee of \$46,000 and was required to make milestone payments upon attainment of certain milestone events, royalties based on net sales of products covered by the patent-related rights and a portion of any sublicense income received by the Company. The Licensor also granted the Company a buy-out option which was exercisable at any time during the term of the agreement at increasing amounts based on the achievement of certain milestones. The Company had the right to terminate the agreement at any time by giving 90 days advance notice subject to the payment of any amounts due under the agreement at that time. Expenses related to the license agreement were recognized in general and administrative expense in the statements of operations.

In July 2021, the Company gave notice to the Licensor of its termination of the license agreement and the license agreement was terminated effective October 14, 2021. The Company has paid to the Licensor the prorated annual fees through the termination date. No milestones had been achieved as of the termination date.

### ***(d) Employment Agreements***

The Company has agreements with its executive officers that provide for severance payments to the employee upon termination of the agreement by the Company for any reason other than for cause, death or disability or by the employee for good reason. The maximum aggregate severance payments under the agreements were approximately \$1,291,900 at December 31, 2022.

### ***(e) Litigation***

The Company is subject, from time to time, to claims by third parties under various legal disputes. The defense of such claims, or any adverse outcome relating to any such claims, could have a material adverse effect on the Company's liquidity, financial condition and cash flows.

During the year ended December 31, 2021, two securities class action complaints were filed against the Company and its executive officers following disclosure of interim results from the AD/PD Trials. Both complaints were voluntarily dismissed without prejudice by the plaintiffs.

At December 31, 2022, the Company did not have any pending legal actions.

***(f) Risks and Uncertainties***

The extent to which the COVID-19 pandemic could have a material impact on the Company's current or future clinical trials is dependent on the spread of the disease and government and healthcare system responses to such spread, which are presently highly uncertain. Management continues to evaluate the potential impact. The financial statements do not include any adjustments that might result from the outcome of this uncertainty.

**(8) Stockholders' Equity**

***(a) Common Stock***

1. Dividends

Subject to the rights of holders of all classes of Company stock outstanding having rights that are senior to or equivalent to holders of common stock, the holders of the common stock are entitled to receive dividends when and as declared by the Board of Directors ("Board").

2. Liquidation

Subject to the rights of holders of all classes of stock outstanding having rights that are senior to or equivalent to holders of common stock as to liquidation, upon the liquidation, dissolution or winding up of the Company, the assets of the Company will be distributed to the holders of common stock.

3. Voting

The holders of common stock are entitled to one vote for each share of common stock held. There is no cumulative voting.

***(b) Preferred Stock***

Preferred stock may be issued from time to time by the Board in one or more series.

***(c) Warrants***

In conjunction with the IPO, the Company granted the underwriters 100,000 warrants to purchase shares of Company common stock at an exercise price of \$7.50 per share, which is 125% of the initial public offering price. The warrants have a five-year term and were exercisable as of January 29, 2021. During the year ended December 31, 2021, 97,600 of the warrants were tendered to the Company by the holders pursuant to cashless exercises. Warrants outstanding as of December 31, 2022 and 2021, were 2,400 and 2,400, respectively. The Company accounts for the warrants as a component of stockholders' equity.

**(9) Stock-Based Compensation**

Effective upon the closing of the Company's IPO on January 31, 2020, the Company's 2019 Equity Incentive Plan (the "2019 Plan") became effective, succeeding the Company's previous equity incentive plan. No new options may be issued under the previous plan, although shares subject to grants which are cancelled or forfeited will again be available under the 2019 Plan. Effective June 1, 2021, the 2019 Plan was amended to increase the number of shares authorized to be issued from 1,000,000 to 2,000,000. As of December 31, 2022, 392,874 shares were available for future grants.

The 2019 Plan provides for grants to employees, members of the Board, consultants and advisors to the Company, in the form of stock options, stock awards and other equity-based awards. The amount and terms of grants are determined by the Board. Stock options have a maximum term of 10 years after date of grant and are exercisable in cash or as otherwise determined by the Board.

Stock-based compensation expense in the statements of operations, including the fair value of stock awards to consultants and advisors for services rendered, for the years ended December 31, 2022 and 2021 was as follows:

	Year Ended December 31,	
	2022	2021
General and administrative .....	\$ 5,778,117	\$ 2,680,882
Research and development.....	3,374,403	2,016,745
	<u>\$ 9,152,520</u>	<u>\$ 4,697,627</u>

Stock option activity for the years ended December 31, 2022, and 2021, was as follows:

	Number of Shares	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value
Outstanding at December 31, 2020 .....	1,111,466	\$ 2.57		
Granted .....	538,095	\$ 33.78		
Exercised .....	(159,813)	\$ 2.83		
Forfeited .....	—	\$ -		
Outstanding at December 31, 2021 .....	1,489,748	\$ 13.82		
Granted .....	348,294	\$ 15.90		
Exercised .....	(70,101)	\$ 1.97		
Forfeited .....	(110,599)	\$ 25.93		
Outstanding at December 31, 2022 .....	<u>1,657,342</u>	\$ 13.95	6.2	\$ 9,907,660
Exercisable at December 31, 2022 .....	<u>1,310,667</u>	\$ 11.64	5.4	\$ 9,591,460

The aggregate intrinsic value of options exercised during the years ended December 31, 2022 and 2021 was \$803,357 and \$11,163,998, respectively. As of December 31, 2022, there was \$4,089,400 unrecognized compensation expense related to unvested options. That cost is expected to be recognized over a weighted-average period of 1.39 years.

During the years ended December 31, 2022 and 2021, the Company issued 348,294 and 538,095 options, respectively. Under the grant agreements for the 2022 stock option grants, 10,000 of the options vested immediately, 9,947 of the options vested on March 29, 2022, 9,947 of the options vest on March 31, 2023, 43,333 of the options vest on August 29, 2023, and 255,067 of the options vest in substantially equal quarterly installments over two years from the date of grant. 20,000 of the options have performance-based vesting conditions. As of December 31, 2022, it was not considered probable that the performance conditions would be achieved, and no compensation expense was recognized during the period related to these options. Under the grant agreements for the 2021 stock option grants, 143,391 of the options vested immediately, 155,253 of the options vested on March 31, 2022, 155,251 of the options vest on March 31, 2023 and 84,200 of the options vest in substantially equal quarterly installments over two years from the date of grant. All of the options have a 10-year term.

The weighted average grant date fair value of options issued during the years ended December 31, 2022 and 2021 was \$13.24 per share and \$27.13 per share, respectively. The fair value was estimated using the Black Sholes option pricing model. The expected life of options was estimated using the simplified method, as the Company has limited historical information to develop reasonable expectations about future exercise patterns and post-vesting employment. The risk-free rate was based on the interest rate payable on U.S. Treasury securities at the time of grant for a period that is commensurate with the expected term of the option. Given the lack of

a public market for the Company's common stock prior to the IPO, the expected stock price volatility was based on a weighted approach that incorporates the historic daily volatility of the Company's common stock since the IPO and the historic daily volatility of similar companies that have been publicly traded for a period commensurate with the expected term of the option. The expected dividend yield is 0% because the Company has not historically paid and does not expect for the foreseeable future to pay a dividend on its common stock. The weighted average assumptions used in the valuation of options granted were as follows:

	Year Ended December 31, 2022	Year Ended December 31, 2021
Risk-free interest rate . . . . .	2.24 %	1.17 %
Expected life . . . . .	5.9	5.3
Expected volatility . . . . .	112 %	113 %
Expected dividend yield . . . . .	—	—

During the year ended December 31, 2022, previously issued stock options were modified for an employee who is no longer employed with the Company. As a result of this modification, \$1,219,572 was recognized as stock option modification expense and included in general and administrative expenses on the accompanying statement of operations.

#### (10) Net Loss Per Share

The Company has reported a net loss for the years ended December 31, 2022 and 2021, and the basic and diluted net loss per share attributable to common stockholders are the same for both years because all warrants and stock options have been excluded from the computation of diluted weighted-average shares outstanding because such securities would have an antidilutive impact.

The following table sets forth the computation of basic and diluted net loss per share:

	Year Ended December 31,	
	2022	2021
Numerator		
Net loss . . . . .	<u>\$ (25,328,567)</u>	<u>\$ (14,487,132)</u>
Denominator		
Weighted-average common shares outstanding, basic and diluted . . . . .	8,162,326	7,626,278
Net loss per share, basic and diluted . . . . .	\$ (3.10)	\$ (1.90)

Potential common shares that are excluded from the computation of diluted weighted-average shares outstanding are as follows:

	December 31,	
	2022	2021
Stock options . . . . .	1,657,342	1,489,748
Warrants . . . . .	2,400	2,400

#### (11) Income Taxes

The federal and state provision (benefit) for income taxes was \$0 for the years ended December 31, 2022 and 2021.

A reconciliation of income tax provision (benefit) computed at the statutory federal income tax rate to income taxes as reflected in the financial statements for the years ended December 31, 2022 and 2021 is as follows:

	<b>Year Ended December 31,</b>	
	<b>2022</b>	<b>2021</b>
Federal income tax benefit at statutory rate .....	21.0 %	21.0 %
State and local tax, net of federal benefit .....	5.7 %	13.7 %
Permanent differences .....	(1.5)%	0.1 %
Research and development credit .....	3.8 %	2.4 %
Stock-based compensation .....	0.8 %	15.7 %
Change in valuation allowance .....	(29.8)%	(52.9)%
Effective income tax rate .....	<u>0.0 %</u>	<u>0.0 %</u>

Deferred taxes are recognized for temporary differences between the basis of assets and liabilities for financial statement and income tax purposes. The significant components of the Company's deferred tax assets are comprised of the following:

	<b>As of December 31,</b>	
	<b>2022</b>	<b>2021</b>
Net operating loss carryforwards .....	\$ 7,919,085	\$ 6,512,249
Stock compensation .....	3,767,330	1,759,129
Capitalized R&D .....	1,725,622	2,002,431
Section 174 .....	3,445,935	
R&D credit carryforwards .....	1,618,295	648,077
Total deferred tax assets .....	18,476,267	10,921,886
Less valuation allowance .....	(18,476,267)	(10,921,886)
Net deferred taxes .....	<u>\$ —</u>	<u>\$ —</u>

As of December 31, 2022, the Company had U.S. federal net operating loss ("NOL") carryforwards of \$27,536,031 which may be available to offset future income tax liabilities. Federal NOL carryforwards generated in 2017 and prior of \$2,764,240 will expire beginning in 2032. The remaining federal NOL carryforwards generated in 2018 and later do not expire. As of December 31, 2022, the Company also had U.S. state NOL carryforwards of \$30,082,914 which may be available to offset future income tax liabilities and will expire beginning in 2028.

The Company has recorded a full valuation allowance against its net deferred tax assets as of December 31, 2022 and 2021 because the Company has determined that it is more likely than not that these assets will not be fully realized due to historic net operating losses incurred. The Company experienced a net change in valuation allowance of \$7,554,381 and \$7,672,071 in the years ended December 31, 2022 and 2021, respectively.

As of December 31, 2022, the Company had federal research and development tax credit carryforwards of \$1,618,294 available to reduce future tax liabilities which expire beginning in 2028.

Under the provisions of the Internal Revenue Code, the NOL and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. NOL and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant stockholders over a three-year period in excess of 50%, as defined under Sections 382 and 383 of the Internal Revenue Code as well as similar state provisions. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. The Company has completed financings since its inception which may have resulted in a change in control as defined by Sections 382 and 383 of the Internal Revenue Code, or could result in a change in control in the future.

The Company files tax returns as prescribed by the tax laws of the jurisdictions in which it operates. In the normal course of business, the Company is subject to examination by federal and state jurisdictions, where applicable. The Company's tax years from

2019 to the present remain open for review. All open years may be examined to the extent that tax credits or NOL carryforwards are used in future periods. The Company will recognize interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2022, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in the Company's statements of operations.

Effective for tax years beginning after December 31, 2021, taxpayers are required to capitalize any expenses incurred that are considered incidental to research and experimentation (R&E) activities under IRC Section 174. While taxpayers historically had the option of deducting these expenses under IRC Section 174, the December 2017 Tax Cuts and Jobs Act mandates capitalization and amortization of R&E expenses for tax years beginning after December 31, 2021. Expenses incurred in connection with R&E activities in the US must be amortized over a 5-year period if incurred, and R&E expenses incurred outside the US must be amortized over a 15-year period. R&E activities are broader in scope than qualified research activities considered under IRC Section 41 (relating to the research tax credit). For the year ended December 31, 2022, the Company performed an analysis based on available guidance and determined that it will continue to be in a loss position even after the required capitalization and amortization of its R&E expenses. The Company will continue to monitor this issue for future developments, but it does not expect R&E capitalization and amortization to require it to pay cash taxes now or in the near future.

## **(12) Restatement of Previously Issued Unaudited Condensed Financial Statements**

During its preparation of its 2022 audited combined financial statements and notes thereto, the Company concluded that there were material research and development expenses and related balance sheet errors in its previously issued unaudited condensed financial statements as of and for each of the quarterly and year to date periods ended March 31, 2022, June 30, 2022 and September 30, 2022, primarily relating to the timing of payments for research and development expenses and recognition of expenses.

The Company noted the following items were improperly expensed during the three months ended March 31, 2022:

- Payments, in the amount of \$800,840, were improperly recorded in research and development expenses during the three months ended March 31, 2022. These amounts should have been recorded as prepaid expenses and other current assets as of March 31, 2022.
- Research and development expense amounts totaling \$140,690 were not recorded during the three months ended March 31, 2022. This amount should have been recorded in accrued expenses and other current liabilities as of March 31, 2022.

These errors in the accounting for research and development expenses resulted in an understatement of prepaid assets and other current assets of \$800,840, accrued expenses and other current liabilities of \$140,690 and an overstatement of operating expenses and net loss of \$660,150 as of and for the three months ended March 31, 2022.

The Company noted the following items were improperly expensed during the three and six months ended June 30, 2022:

- Payments, in the amount of \$2,883,977 were improperly recorded in research and development expenses during the three months ended June 30, 2022. These amounts should have been recorded in prepaid expenses and other current assets as of June 30, 2022. Additionally, \$102,232 was expensed during the three months ended June 30, 2022 related to the prior quarter restatements.

These errors, including the errors from the three months ended March 31, 2022, in the accounting for research and development expenses resulted in a cumulative understatement of prepaid assets and other current assets of \$3,441,895, as of June 30, 2022, and an overstatement operating expenses and net loss of \$2,781,745 and \$3,441,895 for the three and six months ended June 30, 2022, respectively.

The Company noted the following items were improperly expensed during the three and nine months ended September 30, 2022:

- Payments, in the amount of \$1,320,321, were improperly recorded in research and development expenses during the three months ended September 30, 2022. These amounts should have been recorded in prepaid expenses and other current assets as of September 30, 2022. Additionally, \$130,826 was expensed during the three months ended September 30, 2022 related to the prior quarter restatements.

These errors, including the errors from the six months ended June 30, 2022, in the accounting for research and development expenses resulted in an understatement of prepaid assets and other current assets of \$4,631,390 as of September 30, 2022, and an overstatement of operating expenses and net loss of \$1,189,495 and \$4,631,390 for the three and nine months ended September 30, 2022, respectively.

As a result of such errors, the Company concluded that the previously issued 2022 unaudited condensed financial statements were materially misstated and has restated herein our previously issued unaudited condensed financial statements for each interim period within the fiscal year ended December 31, 2022. The restatement corrections impact certain components within operating cash flows of the unaudited condensed statements of cash flows. Total operating cash flows, investing activities, financing activities, and cash and cash equivalents are unchanged as a result of the restatements and as a result are not restated herein.

The following tables present the amounts previously reported, the restatement impact and the amount as restated. The 2022 quarterly restatements will be effective with the filing of our future 2023 unaudited interim condensed financial statement filings in Quarterly Reports on Form 10-Q.

The values as previously reported for the fiscal quarters ended September 30, 2022, June 30, 2022, and March 31, 2022 were derived from our Quarterly Reports on Form 10-Q filed on November 8, 2022, August 8, 2022 and May 4, 2022, respectively.



**Annovis Bio, Inc.**  
**Balance Sheets**

	<b>As of March 31, 2022</b>		
	<b>As Reported</b>	<b>(unaudited) Restatement Impacts</b>	<b>As Restated</b>
<b>Assets</b>			
Current assets:			
Cash and cash equivalents . . . . .	\$ 42,668,838	\$ —	\$ 42,668,838
Prepaid expenses and other current assets . . . . .	627,902	800,840	1,428,742
Deferred clinical materials . . . . .	—	—	—
Total current assets . . . . .	<u>43,296,740</u>	<u>800,840</u>	<u>44,097,580</u>
Total Assets . . . . .	<u>\$ 43,296,740</u>	<u>\$ 800,840</u>	<u>\$ 44,097,580</u>
<b>Liabilities and Stockholders' Equity</b>			
Current liabilities:			
Accounts payable . . . . .	\$ 928,997	\$ —	\$ 928,997
Accrued expenses . . . . .	327,435	140,690	468,125
Total current liabilities . . . . .	<u>1,256,432</u>	<u>140,690</u>	<u>1,397,122</u>
Total liabilities . . . . .	<u>\$ 1,256,432</u>	<u>\$ 140,690</u>	<u>\$ 1,397,122</u>
Commitments and contingencies (Note 7)			
Stockholders' equity:			
Preferred stock – \$0.0001 par value, 2,000,000 shares authorized and 0 shares issued and outstanding . . . . .	—	—	—
Common stock – \$0.0001 par value, 35,000,000 shares authorized and 8,163,923 and 8,100,570 shares issued and outstanding at March 31, 2022 and December 31, 2021, respectively . . . . .	816	—	816
Additional paid-in capital . . . . .	76,659,912	—	76,659,912
Accumulated deficit . . . . .	<u>(34,620,420)</u>	<u>660,150</u>	<u>(33,960,270)</u>
Total stockholders' equity . . . . .	<u>42,040,308</u>	<u>660,150</u>	<u>42,700,458</u>
Total liabilities and stockholders' equity . . . . .	<u>\$ 43,296,740</u>	<u>\$ 800,840</u>	<u>\$ 44,097,580</u>

**Annovis Bio, Inc.**  
**Statements of Operations**  
**(unaudited)**

	<b>Three Months Ended March 31, 2022</b>		
	<b>As Reported</b>	<b>Restatement Impacts</b>	<b>As Restated</b>
Operating expenses:			
Research and development .....	\$ 2,809,791	\$ (660,150)	\$ 2,149,641
General and administrative .....	3,104,071	—	3,104,071
Total operating expenses .....	<u>5,913,862</u>	<u>(660,150)</u>	<u>5,253,712</u>
Operating loss .....	(5,913,862)	660,150	(5,253,712)
Other income:			
Interest income .....	19,649	—	19,649
Grant Income .....	—	—	—
Total other income .....	<u>19,649</u>	<u>—</u>	<u>19,649</u>
Loss before income taxes .....	(5,894,213)	660,150	(5,234,063)
Income tax expense (benefit) .....	—	—	—
Net loss .....	<u>\$ (5,894,213)</u>	<u>\$ 660,150</u>	<u>\$ (5,234,063)</u>
Basic and diluted loss per common share .....	<u>\$ (0.72)</u>	<u>—</u>	<u>\$ (0.64)</u>
Weighted average number of common shares outstanding, basic and diluted .....	<u>8,157,445</u>	<u>—</u>	<u>8,157,445</u>

**Annovis Bio, Inc.**  
**Statements of Cash Flows**  
**(unaudited)**

	<b>Three Months Ended March 31, 2022</b>		
	<b>As Reported</b>	<b>Restatement Impacts</b>	<b>As Restated</b>
Cash flows from operating activities:			
Net loss .....	\$ (5,894,213)	660,150	\$ (5,234,063)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense .....	3,434,944	—	3,434,944
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets .....	(312,438)	(800,840)	(1,113,278)
Accounts payable .....	240,923	—	240,923
Accrued expenses .....	(491,005)	140,690	(350,315)
Net cash used in operating activities .....	<u>(3,021,789)</u>	<u>—</u>	<u>(3,021,789)</u>
Cash flows from financing activities:			
Proceeds from exercise of stock options .....	4,613	—	4,613
Net cash used in financing activities .....	<u>4,613</u>	<u>—</u>	<u>4,613</u>
Net (decrease) increase in cash and cash equivalents .....	(3,017,176)	—	(3,017,176)
Cash and cash equivalents, beginning of period. ....	<u>45,686,014</u>	<u>—</u>	<u>45,686,014</u>
Cash and cash equivalents, end of period .....	<u>\$ 42,668,838</u>	<u>—</u>	<u>\$ 42,668,838</u>

**Annovis Bio, Inc.**  
**Balance Sheets**

	<b>As of June 30, 2022</b>		
	<b>As Reported</b>	<b>(unaudited) Restatement Impacts</b>	<b>As Restated</b>
<b>Assets</b>			
Current assets:			
Cash and cash equivalents . . . . .	\$ 35,974,251	\$ —	\$ 35,974,251
Prepaid expenses and other current assets . . . . .	551,072	3,441,895	3,992,967
Deferred clinical materials . . . . .	—	—	—
Total current assets . . . . .	<u>36,525,323</u>	<u>3,441,895</u>	<u>39,967,218</u>
Total Assets . . . . .	<u>\$ 36,525,323</u>	<u>\$ 3,441,895</u>	<u>\$ 39,967,218</u>
<b>Liabilities and Stockholders' Equity</b>			
Current liabilities:			
Accounts payable . . . . .	\$ 901,841	\$ —	\$ 901,841
Accrued expenses . . . . .	397,544	—	397,544
Total current liabilities . . . . .	<u>1,299,385</u>	<u>—</u>	<u>1,299,385</u>
Total liabilities . . . . .	<u>\$ 1,299,385</u>	<u>\$ —</u>	<u>\$ 1,299,385</u>
Commitments and contingencies (Note 7)			
Stockholders' equity:			
Preferred stock – \$0.0001 par value, 2,000,000 shares authorized and 0 shares issued and outstanding . . . . .	—	—	—
Common stock – \$0.0001 par value, 35,000,000 shares authorized and 8,163,923 and 8,100,570 shares issued and outstanding at June 30, 2022 and December 31, 2021, respectively . . . . .	816	—	816
Additional paid-in capital . . . . .	78,563,673	—	78,563,673
Accumulated deficit . . . . .	<u>(43,338,551)</u>	<u>3,441,895</u>	<u>(39,896,656)</u>
Total stockholders' equity . . . . .	<u>35,225,938</u>	<u>3,441,895</u>	<u>38,667,833</u>
Total liabilities and stockholders' equity . . . . .	<u>\$ 36,525,323</u>	<u>\$ 3,441,895</u>	<u>\$ 39,967,218</u>

**Annovis Bio, Inc.**  
**Statements of Operations**  
**(unaudited)**

	<b>Three Months Ended June 30, 2022</b>		
	<b>As Reported</b>	<b>Restatement Impacts</b>	<b>As Restated</b>
Operating expenses:			
Research and development .....	\$ 6,815,708	\$ (2,781,745)	\$ 4,033,963
General and administrative .....	1,938,447	—	1,938,447
Total operating expenses .....	<u>8,754,155</u>	<u>(2,781,745)</u>	<u>5,972,410</u>
Operating loss .....	(8,754,155)	2,781,745	(5,972,410)
Other income:			
Interest income .....	36,024	—	36,024
Grant Income .....	—	—	—
Total other income .....	<u>36,024</u>	<u>—</u>	<u>36,024</u>
Loss before income taxes .....	(8,718,131)	2,781,745	(5,936,386)
Income tax expense (benefit) .....	—	—	—
Net loss .....	<u>\$ (8,718,131)</u>	<u>\$ 2,781,745</u>	<u>\$ (5,936,386)</u>
Basic and diluted loss per common share .....	<u>\$ (1.07)</u>	<u>—</u>	<u>\$ (0.73)</u>
Weighted average number of common shares outstanding, basic and diluted .....	<u>8,163,923</u>	<u>—</u>	<u>8,163,923</u>

**Annovis Bio, Inc.**  
**Statements of Operations**  
**(unaudited)**

	<b>Six Months Ended June 30, 2022</b>		
	<b>As Reported</b>	<b>Restatement Impacts</b>	<b>As Restated</b>
Operating expenses:			
Research and development .....	\$ 9,625,499	\$ (3,441,895)	\$ 6,183,604
General and administrative .....	5,042,518	—	5,042,518
Total operating expenses .....	<u>14,668,017</u>	<u>(3,441,895)</u>	<u>11,226,122</u>
Operating loss .....	(14,668,017)	3,441,895	(11,226,122)
Other income:			
Interest income .....	55,673	—	55,673
Grant Income .....	—	—	—
Total other income .....	<u>55,673</u>	<u>—</u>	<u>55,673</u>
Loss before income taxes .....	(14,612,344)	3,441,895	(11,170,449)
Income tax expense (benefit) .....	—	—	—
Net loss .....	<u>\$ (14,612,344)</u>	<u>\$ 3,441,895</u>	<u>\$ (11,170,449)</u>
Basic and diluted loss per common share .....	<u>\$ (1.79)</u>	<u>—</u>	<u>\$ (1.37)</u>
Weighted average number of common shares outstanding, basic and diluted .....	<u>8,160,702</u>	<u>—</u>	<u>8,160,702</u>

**Annovis Bio, Inc.**  
**Statements of Cash Flows**  
**(unaudited)**

	<b>Six Months Ended June 30, 2022</b>		
	<b>As Reported</b>	<b>Restatement Impacts</b>	<b>As Restated</b>
Cash flows from operating activities:			
Net loss .....	\$ (14,612,344)	3,441,895	\$ (11,170,449)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense .....	5,338,705	—	5,338,705
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets .....	(235,608)	(3,441,895)	(3,677,503)
Accounts payable .....	213,767	\$ 213,767	
Accrued expenses .....	(420,896)	\$ (420,896)	
Net cash used in operating activities .....	<u>(9,716,376)</u>	<u>—</u>	<u>(9,716,376)</u>
Cash flows from financing activities:			
Proceeds from issuance of common stock, net of issuance costs .....	—	—	—
Proceeds from exercise of stock options .....	4,613	—	4,613
Net cash used in financing activities .....	<u>4,613</u>	<u>—</u>	<u>4,613</u>
Net (decrease) increase in cash and cash equivalents .....	<u>(9,711,763)</u>	<u>—</u>	<u>(9,711,763)</u>
Cash and cash equivalents, beginning of period .....	45,686,014	—	45,686,014
Cash and cash equivalents, end of period .....	<u>\$ 35,974,251</u>	<u>—</u>	<u>\$ 35,974,251</u>

**Annovis Bio, Inc.**  
**Balance Sheets**

	<b>As of September 30, 2022</b>		
	<b>(unaudited)</b>		
	<b>As Reported</b>	<b>Restatement Impacts</b>	<b>As Restated</b>
<b>Assets</b>			
Current assets:			
Cash and cash equivalents . . . . .	\$ 31,987,091	\$ —	\$ 31,987,091
Prepaid expenses and other current assets . . . . .	499,947	4,631,390	5,131,337
Total current assets . . . . .	<u>32,487,038</u>	<u>4,631,390</u>	<u>37,118,428</u>
Total Assets . . . . .	<u>\$ 32,487,038</u>	<u>\$ 4,631,390</u>	<u>\$ 37,118,428</u>
<b>Liabilities and Stockholders' Equity</b>			
Current liabilities:			
Accounts payable . . . . .	\$ 1,845,705	\$ —	\$ 1,845,705
Accrued expenses . . . . .	680,830	—	680,830
Total current liabilities . . . . .	<u>2,526,535</u>	<u>—</u>	<u>2,526,535</u>
Total liabilities . . . . .	<u>\$ 2,526,535</u>	<u>\$ —</u>	<u>\$ 2,526,535</u>
Commitments and contingencies (Note 7)			
Stockholders' equity:			
Preferred stock – \$0.0001 par value, 2,000,000 shares authorized and 0 shares issued and outstanding . . . . .	—	—	—
Common stock – \$0.0001 par value, 35,000,000 shares authorized and 8,163,923 and 8,100,570 shares issued and outstanding at September 30, 2022 and December 31, 2021, respectively . . . . .	816	—	816
Additional paid-in capital . . . . .	80,919,684	—	80,919,684
Accumulated deficit . . . . .	(50,959,997)	4,631,390	(46,328,607)
Total stockholders' equity . . . . .	<u>29,960,503</u>	<u>4,631,390</u>	<u>34,591,893</u>
Total liabilities and stockholders' equity . . . . .	<u>\$ 32,487,038</u>	<u>\$ 4,631,390</u>	<u>\$ 37,118,428</u>



**Annovis Bio, Inc.**  
**Statements of Operations**  
**(unaudited)**

	<b>Three Months Ended September 30, 2022</b>		
	<b>As Reported</b>	<b>Restatement Impacts</b>	<b>As Restated</b>
Operating expenses:			
Research and development .....	\$ 5,313,033	\$ (1,189,495)	\$ 4,123,538
General and administrative .....	2,361,299	—	2,361,299
Total operating expenses .....	<u>7,674,332</u>	<u>(1,189,495)</u>	<u>6,484,837</u>
Operating loss .....	(7,674,332)	1,189,495	(6,484,837)
Other income:			
Interest income .....	52,886	—	52,886
Grant Income .....	—	—	—
Total other income .....	<u>52,886</u>	<u>—</u>	<u>52,886</u>
Loss before income taxes .....	(7,621,446)	1,189,495	(6,431,951)
Income tax expense (benefit) .....	—	—	—
Net loss .....	<u>\$ (7,621,446)</u>	<u>\$ 1,189,495</u>	<u>\$ (6,431,951)</u>
Basic and diluted loss per common share .....	<u>\$ (0.93)</u>	<u>—</u>	<u>\$ (0.79)</u>
Weighted average number of common shares outstanding, basic and diluted .....	<u>8,163,923</u>	<u>—</u>	<u>8,163,923</u>

**Annovis Bio, Inc.**  
**Statements of Operations**  
**(unaudited)**

	<b>Nine Months Ended September 30, 2022</b>		
	<b>As Reported</b>	<b>Restatement Impacts</b>	<b>As Restated</b>
Operating expenses:			
Research and development .....	\$ 14,938,532	\$ (4,631,390)	\$ 10,307,142
General and administrative .....	7,403,817	—	7,403,817
Total operating expenses .....	<u>22,342,349</u>	<u>(4,631,390)</u>	<u>17,710,959</u>
Operating loss .....	(22,342,349)	4,631,390	(17,710,959)
Other income:			
Interest income .....	108,559	—	108,559
Grant Income .....	—	—	—
Total other income .....	<u>108,559</u>	<u>—</u>	<u>108,559</u>
Loss before income taxes .....	(22,233,790)	4,631,390	(17,602,400)
Income tax expense (benefit) .....	—	—	—
Net loss .....	<u>\$ (22,233,790)</u>	<u>\$ 4,631,390</u>	<u>\$ (17,602,400)</u>
Basic and diluted loss per common share .....	<u>\$ (2.72)</u>	<u>—</u>	<u>\$ (2.16)</u>
Weighted average number of common shares outstanding, basic and diluted .....	<u>8,161,787</u>	<u>—</u>	<u>8,161,787</u>

**Annovis Bio, Inc.**  
**Statements of Cash Flows**  
**(unaudited)**

	Nine Months Ended September 30, 2022		
	As Reported	Restatement Impacts	As Restated
Cash flows from operating activities:			
Net loss .....	\$ (22,233,790)	4,631,390	\$ (17,602,400)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense .....	7,694,716	—	7,694,716
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets .....	(184,483)	(4,631,390)	(4,815,873)
Accounts payable .....	1,157,631	—	1,157,631
Accrued expenses .....	(137,610)	—	(137,610)
Net cash used in operating activities .....	<u>(13,703,536)</u>	<u>—</u>	<u>(13,703,536)</u>
Cash flows from financing activities:			
Proceeds from issuance of common stock, net of issuance costs .....	—	—	—
Proceeds from exercise of stock options .....	4,613	—	4,613
Net cash used in financing activities .....	<u>4,613</u>	<u>—</u>	<u>4,613</u>
Net (decrease) increase in cash and cash equivalents .....	<u>(13,698,923)</u>	<u>—</u>	<u>(13,698,923)</u>
Cash and cash equivalents, beginning of period .....	45,686,014	—	45,686,014
Cash and cash equivalents, end of period .....	<u>\$ 31,987,091</u>	<u>—</u>	<u>\$ 31,987,091</u>

**(13) Subsequent Events**

On January 18, 2023, the Company granted options to purchase an aggregate of 81,705 shares of common stock at an exercise price of \$13.17 per share to employees, members of the board of directors and consultants to the Company.

## SIGNATURES

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

ANNOVIS BIO, INC.

By: /s/ MARIA MACCECCHINI

Name: Maria Macccecchini

Title: *President and Chief Executive Officer*

## SIGNATURES

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. Each of the undersigned hereby constitute and appoint Maria Macccecchini and Henry Hagopian, and each of them, his or her true and lawful attorneys-in-fact and agents, with full and several power of substitution and resubstitution, for him or her and in his or her name, place and stead in any and all capacities, to sign one or more amendments to this Annual Report on Form 10-K, each in such form as they or any one of them may approve, and to file the same with all exhibits thereto and other documents in connection therewith with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done so that this Annual Report and any amendments shall comply with the Securities Exchange Act of 1934, as amended, and the applicable rules and regulations adopted or issued pursuant thereto, as fully and to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or any of them or their substitute or resubstitute, may lawfully do or cause to be done by virtue hereof.

Signature	Title	Date
<u>/s/ MARIA MACCECCHINI</u> Maria Macccecchini	President and Chief Executive Officer (principal executive officer)	March 31, 2023
<u>/s/ HENRY HAGOPIAN</u> Henry Hagopian	Chief Financial Officer (principal financial and accounting officer)	March 31, 2023
<u>/s/ MICHAEL HOFFMAN</u> Michael Hoffman	Chairman of the Board and Director	March 31, 2023
<u>/s/ CLAUDINE BRUCK</u> Claudine Bruck	Director	March 31, 2023
<u>/s/ REID MCCARTHY</u> Reid McCarthy	Director	March 31, 2023
<u>/s/ MARK WHITE</u> Mark White	Director	March 31, 2023