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, 2021
Or
☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15 (d) OF THE SECURITIES EXCHANGE ACT OF 1934**
Commission File Number 033-80623

Achieve Life Sciences, Inc.

(Exact name of the registrant as specified in its charter)

Delaware	**95-4343413**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**

1040 West Georgia Street, Suite 1030, Vancouver, B.C. V6E 4H1
(Address of principal executive offices, including zip code)

(604) 210-2217
(Registrant's telephone number, including area code)
Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	**Trading Symbol(s)**	**Name of Exchange on Which Registered**
Common Stock, par value $0.001 per share	ACHV	The NASDAQ Capital Market

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

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

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

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

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

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

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

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

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

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

As of June 30, 2021, the aggregate market value of the registrant's Common Stock held by non-affiliates of the registrant was $ 84,749,980 computed with reference to the price at which the Common Stock was last sold on June 30, 2021. As of March 10, 2022, 9,460,835 shares of the registrant's Common Stock were outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's Definitive Proxy Statement for its 2021 Annual Meeting of Stockholders ("Proxy Statement"), to be filed within 120 days of the Registrant's fiscal year ended December 31, 2021, is incorporated by reference into Part III of this Annual Report on Form 10-K.

Auditor Name: PricewaterhouseCoopers LLP Auditor Location: Vancouver, BC, Canada

Achieve Life Sciences, Inc.

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PART I

References in this Form 10-K to "Achieve Life Sciences," "Achieve," the "Company," "we," "us" or "our" refer to Achieve Life Sciences, Inc. and its wholly owned subsidiaries. The information in this Annual Report on Form 10-K contains certain forward-looking statements, including statements related to clinical trials, regulatory approvals, markets for our products, new product development, capital requirements and trends in our business that involve risks and uncertainties. Our actual results may differ materially from the results discussed in the forward-looking statements. Factors that might cause such a difference include those discussed in "Business," "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations," as well as those discussed elsewhere in this Annual Report on Form 10-K.

ITEM 1. BUSINESS

OVERVIEW OF OUR BUSINESS AND RECENT DEVELOPMENTS

We are a clinical-stage pharmaceutical company committed to the global development and commercialization of cytisinicline for smoking cessation and nicotine addiction. With more than one billion smokers globally and over 34 million smokers in the United States alone, smoking remains the leading cause of preventable disease and death, responsible for more than eight million deaths annually worldwide. Our primary focus is to address this global epidemic.

We also plan to expand our focus to address other methods of nicotine addiction such as e-cigarettes/vaping The use of e-cigarettes continues to be widespread, with most recent reports from the Centers for Disease Control and Prevention indicating nearly 11 million adult users in the United States alone in 2019. While e-cigarettes have been historically viewed as less harmful than combustible cigarettes, their long-term safety remains controversial. In a recent study that we conducted surveying approximately 500 users of nicotine vaping devices or e-cigarettes, approximately 73% of participants responded that they intend to quit vaping within the next three to 12 months. Of those who intended to quit even sooner, within the next 3 months, more than half stated they would be extremely likely to try a new prescription product to help them do so. We believe that cytisinicline, if approved, could be the first prescription drug indicated for vape and e-cigarette users who are ready to quit their nicotine addiction.

Our management team has significant experience in growing emerging companies focused on the development of under-utilized pharmaceutical compounds to meet unmet medical needs. We intend to use this experience to develop and ultimately commercialize cytisinicline either directly or via strategic collaborations.

Cytisinicline is an established smoking cessation treatment that has been approved and marketed in Central and Eastern Europe by Sopharma AD for over 20 years. Sopharma's marketed product is a 1.5 mg cytisinicline dosage administered on a declining titration schedule over a 25 day period. We are evaluating an improved dosing and administration of cytisinicline that is expected to improve compliance and outcomes for smokers. We have an exclusive license and supply agreement with Sopharma for the development and commercialization of cytisinicline outside of Sopharma's territories which are predominately located in Central and Eastern Europe. It is estimated that over 20 million people have used Sopharma's cytisinicline product to help treat nicotine addiction, including over 2,700 smokers in investigator-conducted, Phase 3 clinical trials in Europe and New Zealand.

Cytisinicline is a naturally occurring, plant-based alkaloid. Cytisinicline is structurally similar to nicotine and has a well-defined, dual-acting mechanism of action that is both agonistic and antagonistic. It is believed to aid in smoking cessation and the treatment of nicotine addiction by interacting with nicotine receptors in the brain by reducing the severity of nicotine withdrawal symptoms through agonistic effects on nicotine receptors and by reducing the reward and satisfaction associated with nicotine through antagonistic properties.

In 2018, the U.S. Adopted Names Council adopted cytisinicline as the non-proprietary, or generic, name for the substance also known as cytisine.

Cytisinicline Ongoing and Recent Clinical Developments

Clinical Trials

Ongoing Company-Sponsored Phase 3 Clinical Trials
In October 2020, we initiated the Phase 3 ORCA-2 clinical trial. ORCA-2 is evaluating the efficacy and safety of 3 mg cytisinicline dosed three times daily compared to placebo in adult smokers at 17 clinical sites in the United States. ORCA-2 participants have been randomized to one of three study arms to determine the smoking cessation efficacy and safety profile of cytisinicline when

administered for either 6 or 12 weeks, compared to placebo. All subjects receive standard behavioral support and have been assigned to one of the following groups:

- Arm A: 12 weeks of placebo
- Arm B: 6 weeks of cytisinicline, followed by 6 weeks of placebo
- Arm C: 12 weeks of cytisinicline

The primary outcome measure of success in the ORCA-2 trial is biochemically verified continuous abstinence during the last 4 weeks of treatment in the 6 and 12-week cytisinicline treatment arms compared to placebo. Each treatment arm will be compared independently to the placebo arm, and the trial will be determined to be successful if either or both of the cytisinicline treatment arms show a statistical benefit compared to placebo. Secondary outcome measures will be conducted to assess continued abstinence rates through 6 months from the start of study treatment. In January 2022, we announced that the last study follow-up visit for the last subject enrolled in the trial was completed in December 2021. A total of 810 adult smokers were randomized. Topline ORCA-2 data results are expected to be reported during the second quarter of 2022.

In January 2022, we initiated our Phase 3 ORCA-3 clinical trial. ORCA-3 is a confirmatory Phase 3 trial required for registrational approval of cytisinicline in the United States. The Phase 3 trial will evaluate the efficacy and safety of 3 mg cytisinicline dosed 3 times daily compared to placebo in 750 adult smokers at 15 clinical sites. ORCA-3 participants will be randomized to one of three study arms to evaluate cytisinicline administered for either 6 or 12 weeks, compared to placebo. All subjects will receive standard behavioral support and will be assigned to one of the following groups:

- Arm A: 12 weeks of placebo
- Arm B: 6 weeks of cytisinicline, followed by 6 weeks of placebo
- Arm C: 12 weeks of cytisinicline

The primary outcome measure of success in the ORCA-3 trial is biochemically verified continuous abstinence during the last four weeks of treatment in the 6 and 12-week cytisinicline treatment arms compared with placebo. Each treatment arm will be compared independently to the placebo arm, and the trial will be determined to be successful if either or both of the cytisinicline treatment arms show a statistical benefit compared to placebo. Secondary outcome measures will be conducted to assess continued abstinence rates through 6 months from the start of study treatment.

Completed Company-Sponsored Phase 2 Clinical Trial

In June 2019, we announced positive top line results for the Phase 2b ORCA-1 trial and defined the dose selection of 3 mg, three times daily, or TID, for our Phase 3 development. ORCA-1 was the first trial in our Ongoing Research of Cytisinicline for Addiction Program, or ORCA Program, that aims to evaluate the effectiveness of cytisinicline for smoking cessation, nicotine addiction therapy, and potential benefit in other indications.

ORCA-1 was initiated in October 2018 and evaluated 254 smokers in the United States. The trial evaluated both 1.5 mg and 3 mg doses of cytisinicline on the standard declining titration schedule as well as a more simplified TID dosing schedule, both over 25 days. The trial was randomized and blinded to compare the effectiveness of the cytisinicline doses and schedules to respective placebo groups. Subjects were treated for 25 days, provided behavioral support, and followed up for an additional four weeks to assess continued smoking abstinence after the 25-day treatment.

The primary endpoint in the study was the reduction in daily smoking, a self-reported measure. Three of the four cytisinicline treatment arms demonstrated a statistically significant reduction, $p<0.05$, compared to placebo. The fourth arm trended to significance ($p= 0.052$). Across all treatment arms, over the 25-day treatment period, subjects on cytisinicline experienced a 74-80% median reduction in the number of cigarettes smoked, compared to a 62% reduction in the placebo arms.

The secondary endpoint of the trial was a 4-week continuous abstinence rate, which is the relevant endpoint for regulatory approval. All cytisinicline treatment arms showed significant improvements in abstinence rates compared to the placebo arms. The most impressive results were observed in the 3 mg TID cytisinicline arm which demonstrated a 50% abstinence rate at week 4, compared to 10% for placebo ($p<0.0001$) and a continuous abstinence rate, weeks 5 through 8, of 30% for cytisinicline compared to 8% for placebo ($p= 0.005$). Smokers in the 3 mg TID arm had an odds ratio of 5.04 (95% CI: 1.42, 22.32) for continuous abstinence from week 5 to week 8, compared with placebo. The odds ratio, or OR, is a standard measure of association between an exposure (cytisinicline treatment) and an outcome (continuous smoking abstinence) such that in this study, smokers receiving 3 mg cytisinicline TID were 5 times more likely to stop smoking compared to subjects on placebo.

At week 4, all four cytisinicline arms demonstrated statistically significant ($p<0.05$) reductions in expired carbon monoxide, or CO, a biochemical measure of smoking activity. Expired CO levels had declined by a median of 71-80% in the cytisinicline treatment arms, compared to only 38% in the placebo arms. The greater reductions in expired CO levels for the cytisinicline arms versus placebo suggest that placebo-treated subjects may have over-reported their reduction in cigarettes smoked or overcompensated with greater inhalation while smoking fewer cigarettes.

Cytisinicline was well-tolerated with no serious adverse effects, or SAEs, reported. The most commonly reported (>5%) adverse effects, or AEs, across all cytisinicline treatment arms versus placebo arms were abnormal dreams, insomnia, upper respiratory tract infections, and nausea. In the 3 mg TID treatment arm versus placebo arms, the most common AEs were abnormal dreams, insomnia, and constipation (each 6% vs 2%), upper respiratory tract infections (6% vs 14%), and nausea (6% vs 10%), respectively. Compliance with study treatment was greater than 94% across all arms.

We presented the ORCA-1 results in September 2019 at the annual European meeting of the Society for Research on Nicotine and Tobacco, or SRNT, held in Oslo, Norway and the trial results were published in the journal Nicotine and Tobacco Research in April 2021. Based on the results of the ORCA-1 trial, we have selected 3 mg TID for Phase 3 development. Overall, the 3 mg dose administered TID demonstrated the best overall safety and efficacy when compared to the 1.5 mg dose or the declining titration schedule evaluated in ORCA-1. At the SRNT European meeting held in September 2021, exploratory analyses were presented that showed cytisinicline treatment had an earlier onset of sustained abstinence compared to placebo and that the cytisinicline TID schedule appeared more effective for achieving sustained abstinence in smokers who had previously failed to quit on varenicline compared to the declining titration schedule.

In November 2019, we held a type C meeting with the U.S. Food and Drug Administration, or FDA, to review the ORCA-1 results and our revisions to the Phase 3 clinical program using the simplified 3 mg TID dosing schedule. The FDA agreed that the 3 mg TID dosing schedule was acceptable.

Recently Completed Investigator-Sponsored Clinical Trial

In June 2020, we announced the topline results from the independent, investigator-sponsored Phase 3 RAUORA trial. RAUORA was a non-inferiority study comparing cytisinicline to Chantix (varenicline) in Māori (indigenous New Zealanders) and whānau (family) of Māori. The study was led by Dr. Natalie Walker, Associate Professor at the University of Auckland, and was funded by the Health Research Council of New Zealand. The study enrollment was planned for 2,140 subjects. In total, 1,105 Māori or whānau expressed interest in participating in the study and a total of 679 were randomized to receive either cytisinicline or varenicline. The average age of participants in the trial was 43 years and approximately 70% of the participants were women.

The study compared cytisinicline administered on a schedule of 25 days of declining titration followed by twice-daily dosing for a total of 12 weeks with varenicline administered on a schedule of seven days of inclining titration followed by twice-daily dosing for a total of 12 weeks. The primary endpoint was a comparison of biochemically confirmed continuous abstinence rates at 6 months, and the trial was designed to assess if the two agents were non-inferior to each other.

The primary endpoint of the non-inferiority trial was to demonstrate that cytisinicline quit rates would be no less than 10% lower than the quit rates for varenicline. Topline results indicated that the RAUORA trial achieved its primary endpoint in showing that cytisinicline plus behavioral support was at least as effective as varenicline plus behavioral support at 6 months. Cytisinicline met the pre-specified non-inferiority endpoint and was trending towards superiority with an Absolute Risk Difference of +4.29 in favor of cytisinicline (95% CI -0.22 to 8.79), demonstrating a 4.29% improvement in quit rates in favor of cytisinicline. Specifically, continuous abstinence rates at 6 months, verified by expired CO, were 12.1% for cytisinicline compared to 7.9% for varenicline. The Relative Risk was 1.55 on an intent-to-treat basis, indicating that subjects in the cytisinicline arm were approximately one and a half times more likely to have quit smoking at 6 months compared to subjects who received varenicline.

Additionally, significantly fewer overall AEs were reported in cytisinicline-treated subjects (Relative Risk 0.56, 95% CI 0.49 to 0.65, $p<0.001$). Notably, of the subjects who experienced adverse events, cytisinicline subjects reported significantly less nausea, insomnia and vivid dreams ($p<0.05$).

The final RAUORA trial results and additional analyses were presented at the SRNT European Annual Meeting in September 2020 and were published in the journal Addiction in March 2021. Also presented at the SRNT Europe Annual Meeting in September 2020 were results from a preclinical study conducted at the University of Cambridge Department of Biochemistry. The study was designed to examine the in vitro binding characteristics of cytisinicline compared to varenicline at the human 5-HT3 receptor. Using a radioligand antagonist displacement design, the study reported an IC50 of 0.50 mM for cytisinicline and 0.25 μM for varenicline, representing a 2000-greater fold agonist binding affinity to the 5-HT3 receptor for varenicline compared to cytisinicline. Agonist activation of 5-HT3 receptors in the brain stem has been shown to induce nausea and vomiting. The data demonstrating the difference

in binding potency at the 5-HT3 receptor provide potential rationale for the lower overall incidence of adverse events reported forcytisinicline compared to varenicline.

Planned Company-Sponsored Phase 2 Clinical Trial

In July 2021, we announced that we were awarded a grant from the National Institute on Drug Abuse, or NIDA, of the National Institutes of Health, or NIH, to evaluate the use of cytisinicline as a treatment for cessation of nicotine e-cigarette use. This initial grant award, in the amount of $320,000, commenced on August 1, 2021, and is being utilized to complete critical regulatory and clinical operational activities, such as protocol finalization, clinical trial site identification, and submission of an Investigational New Drug Application, or IND, to the FDA for investigating cytisinicline in nicotine e-cigarette users. In November 2021, we announced that the FDA has completed their review and accepted the IND application to investigate cytisinicline as a cessation treatment in this population. Following NIH review of completed milestones, and subject to available NIH funding, we expect to receive the next stage of the grant award of approximately $2.5 million, which will enable initiation of the Phase 2 ORCA-V1 clinical study, which we anticipate to occur in the second quarter of 2022, to evaluate cytisinicline in approximately 150 adult nicotine e-cigarette users in the United States. The full grant award of $2.8 million is expected to cover approximately half of the ORCA-V1 clinical study costs. The Primary Investigators for the grant are our Chief Medical Officer, Dr. Cindy Jacobs, and Dr. Nancy Rigotti, Professor of Medicine at Harvard Medical School and Director, Tobacco Research and Treatment Center, Massachusetts General Hospital.

Non-clinical

Non-clinical toxicology studies were sponsored by the National Center for Complementary and Integrative Health, or NCCIH, a division of the NIH and by the National Cancer Institute, or NCI, to assist in our IND for investigating cytisinicline as a smoking cessation treatment. We filed this IND application for cytisinicline with the FDA in 2017, which included the NCCIH sponsored non-clinical studies. Additional NCCIH and NCI sponsored non-clinical toxicology studies were later submitted in support for initiating our Phase 3 program.

Non-clinical toxicology studies that will be required for a New Drug Application, or NDA, include two longer-term chronic toxicology studies and two carcinogenicity studies, which are in distinct stages of execution as company-sponsored studies. Two chronic toxicology studies have been completed and submitted to the FDA. Additionally, one of two carcinogenicity studies has been completed, while the second carcinogenicity study is currently in progress.

OUR PRODUCT CANDIDATE - CYTISINICLINE

Overview of Cytisinicline

Our product candidate, cytisinicline, is a naturally occurring, plant-based alkaloid. Cytisinicline is structurally similar to nicotine and has a well-defined, dual-acting mechanism of action that is both agonistic and antagonistic. It is believed to aid in smoking cessation and the treatment of nicotine addiction by interacting with nicotine receptors in the brain by reducing the severity of nicotine withdrawal symptoms through agonistic effects on nicotine receptors and by reducing the reward and satisfaction associated with nicotine through antagonistic properties.

Cytisinicline is an established smoking cessation treatment that has been approved and marketed in Central and Eastern Europe by Sopharma AD for over 20 years. We have an exclusive license and supply agreement with Sopharma for the development and commercialization of cytisinicline outside of Sopharma's territories which are predominately located in Central and Eastern Europe. It is estimated that over 20 million people have used Sopharma's cytisinicline product to help treat nicotine addiction, including over 2,700 smokers in investigator-conducted, Phase 3 clinical trials in Europe and New Zealand. These trials were published in the New England Journal of Medicine in September 2011 and December 2014 and the journal Addiction in March 2021.

Cytisinicline Mechanism of Action

Cytisinicline is a partial agonist that binds with high affinity to the alpha-4 beta-2, or α4β2, nicotinic acetylcholine receptors in the brain. Through dual-acting partial agonist/partial antagonist activity, cytisinicline is believed to help reduce nicotine cravings, withdrawal symptoms and reward and satisfaction associated with smoking. The α4β2 nicotinic receptor is a well-understood target in addiction. When nicotine binds to this receptor, it causes dopamine to be released in the mid-brain, reinforcing the dopamine reward system. This receptor has been implicated in the development and maintenance of nicotine addiction. Cytisinicline is believed to act as a partial agonist at the α4β2 nicotinic receptor, preventing nicotine from binding and releasing dopamine.

Cytisinicline Opportunity

We have an exclusive license and supply agreement with Sopharma for the development and commercialization of cytisinicline outside of Sopharma's territory, which consists of certain countries in Central and Eastern Europe, Scandinavia, North Africa, the Middle East and Central Asia, as well as Vietnam. We intend to develop and commercialize cytisinicline in the United States, and thereafter to target other markets outside of Sopharma's territory, such as Western Europe, Japan, China, Australasia, Southeast Asia and Latin and South America.

We are developing cytisinicline as an aid to smoking cessation and treatment for nicotine addiction to address the limitations of both prescription drugs and of Over-the-Counter, or OTC, products. We believe that a substantial market exists in the United States, European Union, or EU, and the rest of the world for a safe and effective smoking cessation treatment. We believe cytisinicline can serve as a cost-effective alternative to existing treatments, with the potential for better efficacy than nicotine replacement therapies, or NRTs, and a potentially superior side effect profile than existing prescription smoking cessation products. Our goal is to obtain approval from the FDA and from other regulatory agencies for the sale and distribution of cytisinicline in the United States and subsequently to other countries outside of Sopharma's territory.

Cytisinicline Clinical Development

Non-clinical toxicology studies were sponsored by the National Center for Complementary and Integrative Health, or NCCIH, a division of the National Institutes of Health, or NIH, and by the National Cancer Institute, or NCI, to assist in our Investigational New Drug Application, or IND. In June 2017, we filed our IND application for cytisinicline with the United States Food and Drug Administration, or FDA, which included the NCCIH sponsored non-clinical studies. Additional non-clinical reproductive toxicology studies have also been conducted by NCCIH and NCI, with three such studies already submitted to the FDA. Other non-clinical toxicology studies that will be required for a NDA include two longer-term chronic toxicology studies and two carcinogenicity studies, which are in distinct stages of execution as company sponsored studies. The two chronic toxicology studies have been completed with both study reports submitted to FDA. Additionally, one of the carcinogenicity studies has been completed, while the second carcinogenicity study is in progress and estimated to be completed in 2022.

In August 2017, we initiated a Phase 1 clinical study evaluating the effect of food on the bioavailability of cytisinicline in normal healthy volunteers. We completed the food effect study and announced the results in November of 2017 demonstrating similar bioavailability of cytisinicline in fed and fasted subjects.

In October 2017, we initiated a clinical study assessing the repeat-dose pharmacokinetics, or PK, and pharmacodynamics, or PD, effects of 1.5 mg and 3 mg cytisinicline in 26 healthy volunteer smokers when administered over the 25-day declining titration course of treatment as marketed by Sopharma in their territories. Final results were presented at the Annual Meeting of the Society for Research on Nicotine and Tobacco, or SRNT, in February 2019. All 26 subjects completed the study. Predictable increases in plasma cytisinicline concentrations were observed with increasing unit dosing from 1.5 mg to 3 mg. Smokers in the study were not required to have a designated or predetermined quit date. Overall, subjects had an 80% reduction in cigarettes smoked, 82% reduction in expired CO, and 46% of the subjects achieved biochemically verified smoking abstinence by day 26. Subjects who received 3 mg cytisinicline over the 25 days had a trend for higher smoking abstinence compared to subjects who received 1.5 mg cytisinicline. The AEs observed were mostly mild with transient headaches as the most commonly reported event. No SAEs were observed in the study.

In December 2017, we initiated a series of drug metabolism, drug-to-drug interaction, and transporter studies of cytisinicline and results from these studies were announced in June 2018. These studies demonstrated that cytisinicline has no clinically significant interaction with any of the hepatic enzymes commonly responsible for drug metabolism nor clinically significant interaction with drug transporters. This suggests that cytisinicline may be administered with other medications without the need to modify the dose of any co-administered medications. We will continue to evaluate any new FDA guidance on whether additional drug-to-drug interactions studies will be required prior to a future NDA filing.

We have met with the FDA to identify the steps required for the approval ofcytisinicline. We held an end of Phase 2 meeting with the FDA in May 2018 to review and receive guidance on our Phase 3 clinical program and overall development plans for cytisinicline to support an NDA. This review included submitted results from non-clinical studies, standard drug-to-drug interaction and reproductive/teratogenicity studies. Detailed plans for chronic toxicology, carcinogenicity studies, and additional clinical studies regarding renal impairment, QT interval prolongation, longer term exposure and adequate demonstration of safety and efficacy from our planned randomized, placebo-controlled, Phase 3 clinical trials were also discussed.

In 2018, Sopharma commercially launched a newly formulated cytisinicline tablet with improved shelf life in their territories. In May 2018, we initiated a study to evaluate the effect of food on the bioavailability of cytisinicline in volunteer smokers using this new formulation and data results were announced in September 2018. The study demonstrated similar bioavailability of cytisinicline in fed and fasted subjects. Cytisinicline was extensively absorbed after oral administration with maximum cytisinicline concentration levels observed in the blood within less than two hours with or without food. Total excretion levels of cytisinicline also remained equivalent in both the fed and fasted states, and the 3 mg dose using this new formulation of cytisinicline was well tolerated.

In the third quarter of 2018, the United States Adopted Names Council adopted cytisinicline as the non-proprietary, or generic, name for the substance also known as cytisine.

In December 2018, we announced that the FDA agreed with our Initial Pediatric Study Plan, specifically, providing a full waiver for evaluating cytisinicline in a pediatric population. The reasons for the full waiver were based on the low numbers of children smoking under the age of 12 and the logistical difficulties of recruiting treatment-seeking smokers in the adolescent age group. The agreed upon Initial Pediatric Study Plan is expected to be included as part of our future application for marketing approval of cytisinicline.

In March 2019, we initiated a clinical trial to assess the dose limiting AEs that would define the maximum tolerated dose, or MTD, for a single administered oral dose of cytisinicline. This study evaluated smokers who received one single dose of cytisinicline. The starting dosage of cytisinicline was 6 mg and was to be increased in separate groups of subjects for each escalated dose level until stopping criteria (based on the occurrence of dose-limiting AEs) were reached. A safety review after each dose level was performed by an independent Data Safety Monitor Committee, or DSMC, before escalation to the next dose level. Six dose levels were pre-planned with 21 mg cytisinicline as the highest dose level. When the MTD was not reached at 21 mg, the study was amended to evaluate doses up to 30 mg, as recommended by the DSMC. At this 30 mg dose, the stopping criteria of serious or severe AEs were still not met, but the DSMC recommended stopping the study since the frequency of gastrointestinal symptoms were approaching an MTD level. The results were reviewed with the FDA, with an agreement that further escalation beyond the single 30 mg dose was not required. This Phase-1 study was a requirement for our future NDA and marketing approval of cytisinicline. It fulfills an FDA requirement to evaluate potential safety issues in the event patients exceed a recommended single dose outside of a clinical trial setting.

In June 2019, we announced positive top line results for the Phase 2b ORCA-1 trial and defined the dose selection of 3 mg, three times daily, or TID, for our Phase 3 development. ORCA-1 was the first trial in our ORCA Program that aims to evaluate the effectiveness of cytisinicline for smoking cessation, nicotine addiction, and potential benefit in other indications.

ORCA-1 was initiated in October 2018 and evaluated 254 smokers in the United States. The trial evaluated both 1.5 mg and 3 mg doses ofcytisinicline on the standard declining titration schedule as well as a more simplified TID dosing schedule, both over 25 days. The trial was randomized and blinded to compare the effectiveness of the cytisinicline doses and schedules to respective placebo groups. Subjects were treated for 25 days, provided behavioral support, and followed up for an additional four weeks to assess continued smoking abstinence after the 25-day treatment.

The primary endpoint in the study was the reduction in daily smoking, a self-reported measure. Three of the four cytisinicline treatment arms demonstrated a statistically significant reduction, $p<0.05$, compared to placebo. The fourth arm trended to significance ($p= 0.052$). Across all treatment arms, over the 25-day treatment period, subjects on cytisinicline experienced a 74-80% median reduction in the number of cigarettes smoked, compared to a 62% reduction in the placebo arms.

The secondary endpoint of the trial was a 4-week continuous abstinence rate, which is the relevant endpoint for regulatory approval. All cytisinicline treatment arms showed significant improvements in abstinence rates compared to the placebo arms. The most impressive results were observed in the 3 mg TID cytisinicline arm which demonstrated a 54% abstinence rate starting at week 4, compared to 16% for placebo ($p<0.0001$) and a continuous abstinence rate, weeks 5 through 8, of 30% for cytisinicline compared to 8% for placebo ($p= 0.005$). Participants in the 3 mg TID arm had an OR of 5.04 (95% CI: 1.42, 22.32) for continuous abstinence from week 5 to week 8, compared with placebo indicating that smokers receiving 3 mg cytisinicline TID were 5 times more likely to stop smoking compared to subjects on placebo.

At week 4, all four cytisinicline arms demonstrated statistically significant ($p<0.05$) reductions in expired CO a biochemical measure of smoking activity. Expired CO levels had declined by a median of 71-80% in the cytisinicline treatment arms, compared to only 38% in the placebo arms. The greater reductions in expired CO levels for the cytisinicline arms versus placebo suggest that placebo-treated subjects may have over-reported their reduction in cigarettes smoked or overcompensated with greater inhalation while smoking fewer cigarettes.

Cytisinicline was well-tolerated with no SAEs reported. The most commonly reported (>5%) AEs across all cytisinicline treatment arms versus placebo arms were abnormal dreams, insomnia, upper respiratory tract infections, and nausea. In the 3 mg TID treatment arm versus placebo arms, the most common AEs were abnormal dreams, insomnia, and constipation (each 6% vs 2%), upper respiratory tract infections (6% vs 14%), and nausea (6% vs 10%), respectively. Compliance with study treatment was greater than 94% across all arms.

We presented the ORCA-1 results in September 2019 at the annual European meeting of the Society for Research on Nicotine and Tobacco, or SRNT, held in Oslo, Norway. Based on the results of the ORCA-1 trial, we have selected 3 mg TID for Phase 3 development. Overall, the 3 mg dose administered TID demonstrated the best overall safety and efficacy when compared to other doses and administrations studied in ORCA-1.

In November 2019, we held a type C meeting with the FDA to review the ORCA-1 results and our revisions to the Phase 3 clinical program using the simplified 3 mg TID dosing schedule. The FDA agreed that the 3 mg TID dosing schedule was acceptable. We also discussed with the FDA timing for the submission of the 13-week interim report from the second ongoing chronic toxicology study to support the longer treatment durations of 6- and 12-weeks in the Phase 3 clinical program. This interim chronic toxicology report was submitted in the second quarter of 2020 to the FDA.

In June 2020, we announced topline results from the independent, investigator-sponsored Phase 3 RAUORA trial. RAUORA was a non-inferiority study comparing cytisinicline to Chantix (varenicline) in Māori (indigenous New Zealanders) and whānau (family) of Māori. The study was led by Dr. Natalie Walker, Associate Professor at the University of Auckland, and was funded by the Health Research Council of New Zealand. In total, 1,105 Māori or whānau expressed interest in participating in the study and a total of 679 were randomized to receive either cytisinicline or varenicline. The average age of participants in the trial was 43 years and approximately 70% of the participants were women.

The study compared cytisinicline administered on a schedule of 25 days of declining titration followed by twice-daily dosing for a total of 12 weeks with varenicline administered on a schedule of seven days of inclining titration followed by twice-daily dosing for a total of 12 weeks. The primary endpoint was a comparison of biochemically confirmed continuous abstinence rates at 6 months, and the trial was designed to assess if the two agents were non-inferior to each other.

Topline results indicated that the RAUORA trial achieved statistical significance in showing that cytisinicline plus behavioral support was at least as effective as varenicline plus behavioral support at 6 months. In addition, the trial showed that cytisinicline resulted in significantly fewer reported nausea adverse events as well as significantly fewer overall adverse events when compared to varenicline ($p<0.001$).

The final RAUORA trial results and additional analyses were presented at the SRNT European Annual Meeting in September 2020 and were published in the Journal Addiction in 2021. The primary endpoint of the non-inferiority trial was to demonstrate that cytisinicline quit rates would be no less than 10% lower than the quit rates for varenicline. Results showed that cytisinicline met the pre-specified non-inferiority endpoint and was trending towards superiority with an Absolute Risk Difference of +4.29 in favor of cytisinicline (95% CI -0.22 to 8.79), demonstrating a 4.29% improvement in quit rates in favor of cytisinicline. Specifically, continuous abstinence rates at 6 months, verified by exhaled CO, were 12.1% for cytisinicline compared to 7.9% for varenicline. The Relative Risk was 1.55 on an intent-to-treat basis, indicating that subjects in the cytisinicline arm were approximately one and a half times more likely to have quit smoking at 6 months compared to subjects who received varenicline.

Additionally, significantly fewer overall AEs were reported in cytisinicline-treated subjects (Relative Risk 0.56, 95% CI 0.49 to 0.65, $p<0.001$), indicating that subjects on cytisinicline were roughly half as likely to experience AEs compared to subjects on varenicline. Notably, of the subjects who experienced adverse events (111 in the cytisinicline arm compared to 138 in the varenicline arm), there was significantly less nausea and vivid dreams respectively.

Also presented at the SRNT Europe Annual Meeting in September 2020 were results from a preclinical study conducted at the University of Cambridge Department of Biochemistry. The study was designed to examine the in vitro binding characteristics of cytisinicline compared to varenicline at the human 5-HT3 receptor. Using a radioligand antagonist displacement design, the study reported an IC50 of 0.50 mM for cytisinicline and 0.25 μM for varenicline, representing a 2000-greater fold agonist binding affinity to the 5-HT3 receptor for varenicline compared to cytisinicline. Agonist activation of 5-HT3 receptors in the brain stem has been shown to induce nausea and vomiting. The data demonstrating the difference in binding potency at the 5-HT3 receptor provide potential rationale for the lower overall incidence of adverse events reported for cytisinicline compared to varenicline.

In October 2020, we initiated the Phase 3 ORCA-2 clinical trial. ORCA-2 is evaluating the efficacy and safety of 3 mg cytisinicline dosed three times daily compared to placebo in adult smokers at 17 clinical sites in the United States. ORCA-2 participants have been randomized to one of three study arms to determine the smoking cessation efficacy and safety profile of cytisinicline administered for either 6 or 12 weeks, compared to placebo. All subjects receive standard behavioral support and have been assigned to one of the following groups:

- Arm A: 12 weeks of placebo
- Arm B: 6 weeks of cytisinicline, followed by 6 weeks of placebo
- Arm C: 12 weeks of cytisinicline

The primary outcome measure of success in the ORCA-2 trial is biochemically verified continuous abstinence during the last 4 weeks of treatment in the 6 and 12-week cytisinicline treatment arms compared to placebo. Each treatment arm will be compared independently to the placebo arm, and the trial will be determined to be successful if either or both of the cytisinicline treatment arms show a statistical benefit compared to placebo. Secondary outcome measures will be conducted to assess continued abstinence rates through 6 months from the start of study treatment. In June 2021, we announced that the trial had reached its enrollment target of 750 adult smokers. A total of 810 adult smokers were randomized and the study is closed to further enrollment. Topline ORCA-2 data results are expected to be reported in the second quarter of 2022.

In July 2021, we announced that we were awarded a grant from NIDA of the NIH to evaluate the use of cytisinicline as a treatment for cessation of nicotine e-cigarette use. This initial grant award, in the amount of $320,000, commenced on August 1, 2021, and is being utilized to complete critical regulatory and clinical operational activities, such as protocol finalization, clinical trial site identification, and submission of a new IND to the FDA for investigating cytisinicline in nicotine e-cigarette users. In November 2021, we announced that the FDA has completed their review and accepted the IND application to investigate cytisinicline as a cessation treatment in this population. Following NIH review of completed milestones, and subject to available NIH funding, we expect to receive the next stage of the grant award of approximately $2.5 million, which will enable initiation of the Phase 2 ORCA-V1 clinical study, which we anticipate to occur in the second quarter of 2022, to evaluate cytisinicline in approximately 150 adult nicotine e-cigarette users in the United States. The full grant award of $2.8 million is expected to cover approximately half of the ORCA-V1 clinical study costs. The Primary Investigators for the grant are our Chief Medical Officer, Dr. Cindy Jacobs, and Dr. Nancy Rigotti, Professor of Medicine at Harvard Medical School and Director, Tobacco Research and Treatment Center, Massachusetts General Hospital.

Cytisinicline Clinical Trials

Cytisinicline has been previously tested in in more than 2,700 participants during three large, randomized, independent investigator-sponsored Phase 3 clinical trials using Sopharma's product. These trials were conducted according to Good Clinical Practice, or GCP,

requirements. The objective of these independent groups was to further define the efficacy and safety ofcytisinicline according to GCP standards. Subsequently, we ran the Phase 2b ORCA-1 dose selection trial in 254 smokers in the United States to evaluate the safety and efficacy of alternative cytisinicline dosing and schedules compared to respective placebo groups.

Independent Investigator-Sponsored Clinical Trials

TASC Trial

The Tabex Smoking Cessation, or TASC, trial, was sponsored by the United Kingdom, or U.K., Centre for Tobacco Control Studies and evaluated cytisinicline versus placebo in 740 primarily moderate-to-heavy smokers treated for 25 days in a single center in Warsaw, Poland. The TASC trial was designed as a Real World Evidence trial of cytisinicline that included minimal behavioral support. The primary outcome measure was sustained, biochemically verified smoking abstinence for 12 months after the end of treatment. The TASC trial was conceived by Professor Robert West (Department of Epidemiology and Public Health, University College London) and was funded by a grant from the National Prevention Research Initiative, including contributions from Cancer Research U.K., the U.K. Medical Research Council, U.K. Department of Health and others. We, through Sopharma, provided the study drug used in this trial.

The results of the TASC trial were published in the New England Journal of Medicine in September 2011. The rate of sustained 12-month abstinence was 8.4% in the cytisinicline arm as compared with 2.4% in the placebo group (p=0.001). These results showed that the cytisinicline arm had an OR of 3.4 for sustained 12-month abstinence (the OR standard measure of association between an exposure (cytisinicline treatment) and an outcome (continuous smoking abstinence) in this study, indicated that smokers receiving cytisinicline were 3.4 times more likely to stop smoking compared to placebo for one year). The rate of sustained 6-month abstinence was 10.0% in the cytisinicline arm as compared with 3.5% in the placebo group (p<0.001). Cytisinicline was well tolerated with a slight but significant increase in combined gastrointestinal AEs (upper abdominal pain, nausea, dyspepsia and dry mouth; cytisinicline 51/370 (13.8%) and placebo 30/370 (8.1%). Otherwise, the safety profile of cytisinicline was similar to that of placebo with no other significant differences in the rate of side effects in the two trial arms.

A summary of AEs reported in 10 or more subjects in the TASC trial is included in the table below

TASC - Adverse Events Reported by 10 or More Study Participants[1]

Event	Cytisinicline (N=370)	Placebo (N=370)
	percent (number)	
Any gastrointestinal event	13.8% (51)	8.1% (30)
Upper abdominal pain	3.8 (14)	3.0 (11)
Nausea	3.8 (14)	2.7 (10)
Dyspepsia	2.4 (9)	1.1 (4)
Dry mouth	2.2 (8)	0.5 (2)
Any psychiatric event	4.6% (17)	3.2% (12)
Dizziness	2.2 (8)	1.1 (4)
Somnolence	1.6 (6)	1.1 (4)
Any nervous system event	2.7% (10)	2.4% (9)
Headache	1.9 (7)	2.2 (8)
Skin and subcutaneous tissue	1.6% (6)	1.4% (5)

(1) The incidence of events was analyzed according to the*Medical Dictionary for Regulatory Activities* System Organ Class, or SOC, categorization and preferred terms. Participants who reported more than one event in a system category were counted only once for the category. SOC categories for other events (those reported by fewer than 10 participants) were as follows: general (five events within cytisine and five with placebo), cardiac (four with cytisine and two with placebo), musculoskeletal and connective tissue (three with cytisine and three with placebo), infections (one with placebo), immune system (one with placebo) and metabolism and nutrition (one with placebo).

CASCAID Trial

The second investigator led Phase 3 trial, the Cytisine As a Smoking Cessation Aid, or CASCAID, non-inferiority trial, was sponsored by the Health Research Council of New Zealand and was an open-label trial that randomized 1,310 adult daily heavy smokers. Patients were randomized to receive either cytisinicline for 25 days or NRT for 8 weeks. Both treatment groups were offered low intensity telephone behavioral support during trial treatment. The primary outcome measure was continuous self-reported abstinence from smoking one month after quit date. The CASCAID trial was conducted by the Health Research Council of New Zealand. We, through Sopharma, provided the cytisinicline in the form of commercial Tabex™ used in this trial.

The results of the CASCAID trial, which were published in the New England Journal of Medicine in December 2014, showed that cytisinicline was superior to NRT for smoking cessation and, specifically, that cytisinicline had an OR of 1.43 for sustained six-month abstinence (the OR standard measure of association between an exposure (cytisinicline treatment) and an outcome (continuous smoking abstinence) in this study, indicated that smokers receiving cytisinicline were 1.43 times more likely to stop smoking compared to receiving NRT for six months). The rate of continuous one-month abstinence was 40% in the cytisinicline arm as compared with 31% in the NRT arm ($p<0.001$). A secondary outcome included the rate of continuous six-month abstinence which was 22% in the cytisinicline arm as compared with 15% in the NRT arm ($p=0.002$). Cytisinicline was generally well tolerated, although self-reported AEs were slightly higher in the cytisinicline arm compared with the NRT arm. The most frequent AEs for cytisinicline were nausea and vomiting (30/665 (4.6%)) and sleep disorders (28/665 (4.2%)). Reports of these same AEs in the NRT arm were as follows: nausea and vomiting (2/655 (0.3%)) and sleep disorders (2/655 (0.3%)).

A summary of AEs reported in subjects in the CASCAID trial is included in the table below.

CASCAID - Summary of All-Cause Adverse Events

Event	Cytisinicline (N=655)	NRT (N=655)
	percent (number)	
Participants with any adverse event — % (no.)	31% (204)	20% (134)
Adverse events — % (no.)		
Any	44% (288)	27% (174)
In those who complied with treatment[1]	25% (161)	17% (113)
In those who did not comply with treatment	19% (127)	9% (61)
Participants with serious adverse event — % (no.)	7% (45)	39% (6%)
Serious adverse events — % (no.)[2][3]	9% (56)	7% (45)
Deaths[4]	0.2% (1)	0.2% (1)
Life-threatening events	0	0.2% (1)[5]
Hospitalizations	3% (18)	3% (18)
Otherwise medically important events	6% (37)	4% (25)
Severity of all adverse events — % (no.)[4]		
Mild	21% (139)	12% (78)
Moderate	17% (111)	12% (77)
Severe	6% (38)	3% (19)
Most frequent adverse events — % (no.)[5]		
Nausea and vomiting	5% (30)	0.3% (2)
Sleep disorders	4% (28)	0.3% (2)

(1) In the cytisinicline group, compliance was defined as having taken 80% or more of the required number of tablets within 1 month after the quit date (i.e., 80 or more tablets). In the NRT group, compliance was defined as having used NRT at 1 week and 1 month after the quit date. It was assumed that participants with missing data were not compliant.

(2) A serious event was defined as death, a life-threatening event, an event requiring hospitalization, or otherwise medically important event (i.e., the event does not belong in any of the other categories but may jeopardize the patient and may require medical or surgical intervention to prevent the occurrence of one or more other serious events).

(3) The categories are mutually exclusive.

(4) The severity of events was not medically verified.

(5) The list of most frequent adverse events excludes signs and symptoms of cold and influenza. Adverse events were categorized in accordance with the *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10), Australian Modification.

RAUORA Trial

The third investigator led Phase 3 trial was a non-inferiority study comparing cytisinicline to Chantix (varenicline) in Māori (indigenous New Zealanders) and whānau (family) of Māori. The study was led by Dr. Natalie Walker, Associate Professor at the University of Auckland, and was funded by the Health Research Council of New Zealand. In total, 1,105 Māori or whānau expressed interest in participating in the study and a total of 679 were randomized to receive either cytisinicline or varenicline. The average age of participants in the trial was 43 years and approximately 70% of the participants were women.

The study compared cytisinicline administered on a schedule of 25 days of declining titration followed by twice-daily dosing for a total of 12 weeks with varenicline administered on a schedule of seven days of inclining titration followed by twice-daily dosing for a total of 12 weeks. The primary endpoint was a comparison of biochemically confirmed continuous abstinence rates at 6 months, and the trial was designed to assess if the two agents were non-inferior to each other. We, through Sopharma, provided the cytisinicline in the form of commercial Tabex™ used in this trial.

Topline results indicated that the RAUORA trial achieved statistical significance in showing that cytisinicline plus behavioral support was at least as effective as varenicline plus behavioral support at 6 months. In addition, the trial showed that cytisinicline resulted in significantly fewer reported nausea adverse events as well as significantly fewer overall adverse events when compared to varenicline ($p<0.001$).

The final RAUORA trial results and additional analyses were presented at the SRNT European Annual Meeting in September 2020 and were published in the Journal Addiction in 2021. The primary endpoint of the non-inferiority trial was to demonstrate that cytisinicline quit rates would be no less than 10% lower than the quit rates for varenicline. Results showed that cytisinicline met the pre-specified non-inferiority endpoint and was trending towards superiority with an Absolute Risk Difference of +4.29 in favor of cytisinicline (95% CI -0.22 to 8.79), demonstrating a 4.29% improvement in quit rates in favor of cytisinicline. Specifically, continuous abstinence rates at 6 months, verified by expired CO, were 12.1% for cytisinicline compared to 7.9% for varenicline. The Relative Risk was 1.55 on an intent-to-treat basis, indicating that subjects in the cytisinicline arm were approximately one and a half times more likely to have quit smoking at 6 months compared to subjects who received varenicline.

Additionally, significantly fewer overall AEs were reported in cytisinicline-treated subjects (Relative Risk 0.56, 95% CI 0.49 to 0.65, $p<0.001$). Notably, of the subjects who experienced adverse events (111 in the cytisinicline arm compared to 138 in the varenicline arm), there was significantly less nausea and vivid dreams respectively.

Company-Sponsored Phase 2 Clinical Trial

Phase 2b ORCA-1 Trial

We conducted the Phase 2b ORCA-1 dose selection trial, which was initiated in October 2018 and evaluated 254 smokers in the United States. The trial evaluated both 1.5 mg and 3 mg doses of cytisinicline on the standard declining titration schedule as well as a more simplified TID dosing schedule, both over 25 days. The trial was randomized and blinded to compare the effectiveness of the cytisinicline doses and schedules to respective placebo groups. All subjects were treated for 25 days, provided behavioral support, and followed up for an additional four weeks to assess smoking abstinence.

The primary endpoint in the study was the reduction in daily smoking, a self-reported measure. Three of the four cytisinicline treatment arms demonstrated a statistically significant improvement, $p<0.05$, compared to placebo. The fourth arm trended to significance ($p= 0.052$). Across all treatment arms, over the 25-day treatment period, subjects on cytisinicline experienced a 74-80% median reduction in the number of cigarettes smoked, compared to a 62% reduction in the placebo arms.

The primary endpoint in the study was the reduction in daily smoking, a self-reported measure. Three of the four cytisinicline treatment arms demonstrated a statistically significant improvement, $p<0.05$, compared to placebo. The fourth arm trended to significance ($p= 0.052$). Across all treatment arms, over the 25-day treatment period, subjects on cytisinicline experienced a 74-80% median reduction in the number of cigarettes smoked, compared to a 62% reduction in the placebo arms.

The secondary endpoint of the trial was a 4-week continuous abstinence rate, which is the relevant endpoint for regulatory approval. All cytisinicline treatment arms showed significant improvements in abstinence rates compared to the placebo arms. The most impressive results were observed in the 3 mg TID cytisinicline arm which demonstrated a 54% abstinence rate starting at week 4, compared to 16% for placebo ($p<0.0001$) and a continuous abstinence rate, weeks 5 through 8, of 30% for cytisinicline compared to 8% for placebo ($p=0.005$). Participants in the 3 mg TID arm had an OR of 5.04 (95% CI: 1.42, 22.32) for continuous abstinence from

week 5 to week 8, compared with placebo indicating that smokers receiving 3 mg cytisinicline TID were 5 times more likely to stop smoking compared to subjects on placebo

At week 4, all four cytisinicline arms demonstrated statistically significant ($p<0.05$) reductions in expired CO, a biochemical measure of smoking activity. Expired CO levels had declined by a median of 71-80% in the cytisinicline treatment arms, compared to only 38% in the placebo arms. The greater reductions in expired CO levels for the cytisinicline arms versus placebo suggest that placebo-treated subjects may have over-reported their reduction in cigarettes smoked or overcompensated with greater inhalation while smoking fewer cigarettes.

Cytisinicline was well-tolerated with no serious AEs reported. The most commonly reported (>5%) AEs across all cytisinicline treatment arms versus placebo arms were abnormal dreams, insomnia, upper respiratory tract infections, and nausea. In the 3 mg TID treatment arm versus placebo arms, the most common AEs were abnormal dreams, insomnia, and constipation (each 6% vs 2%), upper respiratory tract infections (6% vs 14%), and nausea (6% vs 10%), respectively. Compliance with study treatment was greater than 94% across all arms.

A summary of AEs reported in subjects in the ORCA-1 trial is included in the table below

	TID		**Declining Titration**		**Pooled**	
	1.5 mg (n=52)	**3.0 mg (n=50)**	**1.5 mg (n=51)**	**3.0 mg (n=50)**	**Cytisinicline (n=203)**	**Placebo (n=51)**
At least 1 AE	20 (39%)	21 (42%)	29 (57%)	23 (46%)	93 (46%)	24 (47%)
URTI	5 (10%)	3 (6%)	3 (6%)	2 (4%)	13 (6%)	7 (14%)
Abnormal dreams	4 (8%)	3 (6%)	4 (8%)	7 (14%)	18 (9%)	1 (2%)
Nausea	1 (2%)	3 (6%)	5 (10%)	3 (6%)	12 (6%)	5 (10%)
Insomnia	4 (8%)	3 (6%)	3 (6%)	4 (8%)	14 (7%)	1 (2%)
Headache	6 (12%)	2 (4%)	1 (2%)	1 (2%)	10 (5%)	2 (4%)
Fatigue	3 (6%)	1 (2%)	1 (2%)	2 (4%)	7 (3%)	2 (4%)
Constipation	1 (2%)	3 (6%)	0 (0%)	0 (0%)	4 (2%)	1 (2%)

The outcome of the ORCA-1 trial was the selection of 3 mg TID for Phase 3 development. Overall, the 3 mg dose administered TID demonstrated the best overall safety and efficacy when compared to other doses and administrations studies in ORCA-1. The results from ORCA-1 study were published in the journal Nicotine and Tobacco Research in 2021.

Safety Reporting

As cytisinicline has been marketed in Central and Eastern Europe for over 20 years, substantial safety reporting exists for cytisinicline. A recent periodic safety update report for the period of 2015 - 2020 submitted by Sopharma did not show any new safety signals with cytisinicline and there were no changes in expected benefit/risk during the specified period.

OVERVIEW OF MARKET AND TREATMENT

Overview of the Tobacco Epidemic

The World Health Organization, or WHO, estimates that there are approximately 1.3 billion tobacco users globally and that tobacco kills more than 8 million people each year. More than 7 million of those deaths are the result of direct tobacco use, while around 1.2 million are the result of the exposure of non-smokers to second-hand smoke.

Cigarette smoking is responsible for more than 480,000 deaths per year in the United States, including more than 41,000 deaths resulting from exposure to second-hand smoke, which equates to about one in five deaths annually, or 1,300 deaths every day. According to the American Cancer Society, smoking is a direct cause of approximately 80% of lung cancer deaths and is linked to 30% of all cancer deaths in the United States. Smoking remains the single largest preventable cause of death worldwide and in the United States.

The Centers for Disease Control and Prevention, or CDC, estimates that the annual cost of smoking related illnesses in the United States is more than $300 billion in direct medical care and lost productivity. Over 16 million people in the United States are living with a disease caused by smoking. Among these diseases are cancer, heart disease, stroke, lung diseases, diabetes and chronic obstructive pulmonary disease, or COPD, which includes emphysema and chronic bronchitis. Smoking also increases risk for tuberculosis, certain eye diseases and problems of the immune system, including rheumatoid arthritis.

Tobacco smoking is highly addictive and research suggests that nicotine may be as addictive as heroin, cocaine and alcohol. The CDC estimates that more people in the United States are addicted to nicotine than any other drug and reports that, in 2015, nearly 70% of smokers desired to quit and 55% made an attempt to do so in the prior year. Despite the high number of attempts, fewer than one in ten people are successful in their attempt to quit each year. Additionally, up to 60% of people who quit smoking relapse in the first year.

One increasingly popular alternative to smoking is the use of e-cigarettes, or vaping, which deliver liquid nicotine into a mist or vapor which is inhaled. This method of consumption avoids the chemicals that are associated with cigarette smoke but may have other associated health and safety issues. The emerging use of e-cigarettes is contributing to the growing population of people who are addicted to nicotine.

According to an article published by the U.S. Department of Health and Human Services/CDC in November 2020, it is estimated that nearly 11 million adults in the United States are using e-cigarettes. In a recent survey of nicotine e-cigarette users conducted by Achieve and presented at the 2021 SRNT Annual Meeting, 73% of participants stated they intend to quit vaping in the next three to 12 months. Of those who intend to quit vaping in the next three months, they stated they would be “very/extremely likely to try a new prescription product” to help them quit.

The Global Smoking Cessation Market

Coherent Market Insights Report “Smoking Cessation and Nicotine De-addiction Products Market, 2016-2017” estimated that global revenues for smoking cessation and nicotine de-addiction products in 2016 was approximately $12.8 billion including NRTs, e-cigarettes and drug therapy.

DelveInsight’s 2020 Report “Smoking Cessation “Market Insights, Epidemiology and Market Forecast -2030” estimates that global revenues for prescription smoking cessation therapies alone will reach $5.6 billion by 2030.

Two prescription oral treatments for smoking cessation are currently available in the United States: Chantix (varenicline) marketed by Pfizer (as well as generic manufacturers), and Zyban (bupropion), marketed by GlaxoSmithKline (as well as generic manufacturers).

Varenicline requires a three-month treatment period and bupropion is recommended for between 7 and 12 weeks. Both of these prescription treatments have been proven effective in aiding smoking cessation; however, both are also associated with significant side effects and early discontinuations from treatment. Chantix's labeling indicates elevated instances of nausea, abnormal dreams, constipation, flatulence and vomiting may be experienced by Chantix-treated patients compared to placebo-treated patients, and Zyban's labeling discloses potential adverse reactions including insomnia, rhinitis, dry mouth, dizziness, nervous disturbance, anxiety, nausea, constipation, arthralgia and seizures. High uptake into the brain combined with activity at "off target" receptors could be responsible for Chantix's adverse event profile.

In June 2021, Pfizer Inc. halted the distribution of Chantix after heightened levels, above the FDA's acceptable daily intake limit, of nitrosamines were found in some lots of Chantix pills. In September 2021, Pfizer announced a nationwide recall in the United States of all lots of Chantix and have also withdrawn the product in other countries around the globe. Prior to market withdrawal and launch of generic Chantix (varenicline), global sales of branded Chantix peaked at $1.1 billion. Of those sales, approximately 75% were attributable to the U.S. market.

The vast majority of OTC smoking cessation aids are NRTs. NRTs come in many forms, including gums, lozenges and patches, and have been shown to be less effective than prescription drugs. For example, a Cochrane Group independent database review of nicotine receptor partial agonists published in 2016 compared varenicline with a number of NRTs and varenicline has been proven to be more effective than the NRTs, as demonstrated in head-to-head studies.

LICENSE & SUPPLY AGREEMENTS

Sopharma AD

In 2009 and 2010, we entered into a license agreement, or the Sopharma License Agreement, and a supply agreement, or the Sopharma Supply Agreement, with Sopharma, AD, or Sopharma. Pursuant to the Sopharma License Agreement, we were granted access to all available manufacturing, efficacy and safety data related to cytisinicline, as well as a granted patent in several European countries including Germany, France and Italy related to oral dosage forms of cytisinicline. Additional rights granted under the Sopharma License Agreement include the exclusive use of, and the right to sublicense, the trademark Tabex in all territories—other than certain countries in Central and Eastern Europe, Scandinavia, North Africa, the Middle East and Central Asia, as well as Vietnam, where Sopharma or its affiliates and agents already market Tabex—in connection with the marketing, distribution and sale of products. Under the Sopharma License Agreement, we agreed to pay a nonrefundable license fee. In addition, we agreed to make certain royalty payments equal to a mid-teens percentage of all net sales of Tabex branded products in our territory during the term of the Sopharma License Agreement, including those sold by a third party pursuant to any sublicense which may be granted by us. We have agreed to cooperate with Sopharma in the defense against any actual or threatened infringement claims with respect to Tabex. Sopharma has the right to terminate the Sopharma License Agreement upon the termination or expiration of the Sopharma Supply Agreement. The Sopharma License Agreement will also terminate under customary termination provisions including bankruptcy or insolvency and material breach. To date, any amounts paid to Sopharma pursuant to the Sopharma License Agreement have been immaterial.

A cross-license exists between us and Sopharma whereby we grant to Sopharma rights to any patents or patent applications or other intellectual property rights filed by us in Sopharma territories.

On May 14, 2015, we and Sopharma entered into an amendment to the Sopharma License Agreement. Among other things, the amendment to the Sopharma License Agreement reduced the royalty payments payable by us to Sopharma from a percentage in the mid-teens to a percentage in the mid-single digits and extended the term of the Sopharma License Agreement until May 26, 2029.

On July 28, 2017, we and Sopharma entered into the amended and restated Sopharma Supply Agreement. Pursuant to the amended and restated Sopharma Supply Agreement, for territories as detailed in the licensing agreement, we will exclusively purchase all of our cytisinicline from Sopharma, and Sopharma agrees to exclusively supply all such cytisinicline requested by us, and we extended the term to 2037. In addition, we will have full access to the cytisinicline supply chain and Sopharma will manufacture sufficient cytisinicline to meet a forecast for a specified demand of cytisinicline for the five years commencing shortly after the commencement of the agreement, with the forecast to be updated regularly thereafter. Each of us and Sopharma may terminate the Sopharma Supply Agreement in the event of the other party's material breach or bankruptcy or insolvency.

University of Bristol

In July 2016, we entered into a license agreement with the University of Bristol, or the University of Bristol License Agreement. Under the University of Bristol License Agreement, we received exclusive and nonexclusive licenses from the University of Bristol to certain patent and technology rights resulting from research activities into cytisinicline and its derivatives for use in smoking

cessation, including a number of patent applications related to novel approaches tocytisinicline binding at the nicotinic receptor level. Any patents issued in connection with these applications would be scheduled to expire on February 5, 2036, at the earliest.

In consideration of rights granted by the University of Bristol, we agreed to pay amounts of up to $3.2 million, in the aggregate, tied to a financing milestone and to specific clinical development and commercialization milestones resulting from activities covered by the University of Bristol License Agreement. Additionally, if we successfully commercialize product candidates subject to the University of Bristol License Agreement, we are responsible for royalty payments in the low-single digits and payments up to a percentage in the mid-teens of any sublicense income, subject to specified exceptions, based upon net sales of such licensed products.

On January 22, 2018, we and the University of Bristol entered into an amendment to the University of Bristol License Agreement. Pursuant to the amended University of Bristol License Agreement, we received exclusive rights for all human medicinal uses of cytisinicline across all therapeutic categories from the University of Bristol from research activities into cytisinicline and its derivatives. In consideration of rights granted by the amended University of Bristol License Agreement, we agreed to pay an initial amount of $37,500 upon the execution of the amended University of Bristol License Agreement, and additional amounts of up to $1.7 million, in the aggregate, tied to a financing milestone and to specific clinical development and commercialization milestones resulting from activities covered by the amended University of Bristol License Agreement, in addition to amounts under the original University of Bristol License Agreement of up to $3.2 million in the aggregate, tied to specific financing, development and commercialization milestones. Additionally, if we successfully commercialize any product candidate subject to the amended University of Bristol License Agreement or to the original University of Bristol License Agreement, we will be responsible, as provided in the original University of Bristol License Agreement, for royalty payments in the low-single digits and payments up to a percentage in the mid-teens of any sublicense income, subject to specified exceptions, based upon net sales of such licensed products. Up to December 31, 2021, we had paid the University of Bristol $125,000 pursuant to the University of Bristol License Agreement.

Unless otherwise terminated, the University of Bristol License Agreement will continue until the earlier of July 2036 or the expiration of the last patent claim subject to the University of Bristol License Agreement. We may terminate the University of Bristol License Agreement for convenience upon a specified number of days' prior notice to the University of Bristol. The University of Bristol License Agreement will terminate under customary termination provisions including bankruptcy or insolvency or its material breach of the agreement. Under the terms of the University of Bristol License Agreement, we had provided 100 grams of cytisinicline to the University of Bristol as an initial contribution.

Summary of Milestone Obligations by Product Candidate

The following table sets forth the milestones that we may be required to pay to third parties under the license agreements described above. As described above, we will also be required to pay certain revenue-based royalties with respect to our product candidate.

Milestone Obligations to Third Parties	**Amount Payable**
University of Bristol	Up to $4,837,500(1)

(1) Payable in connection with specific financing, development and commercialization milestones.

GOVERNMENT REGULATIONS

We are heavily regulated in most of the countries in which we operate. In the United States, the principal regulating authority is the FDA. The FDA regulates the safety and efficacy of product candidates and research, quality, manufacturing processes, product approval and promotion, advertising and product labeling. In the EU, the European Medicines Agency, or EMA, and national regulatory agencies regulate the scientific evaluation, supervision and safety monitoring of product candidates, and oversee the procedures for approval of drugs for the EU and European Economic Area, or EEA, countries similar regulations exist in most other countries, and in many countries the government also regulates prices. Health authorities in many middle- and lower-income countries require marketing approval by a recognized regulatory authority, such as the FDA or EMA, before they begin to conduct their application review process and/or issue their final approval.

United States

We intend to focus initially on clinical development of cytisinicline in the United States. It is anticipated that cytisinicline tablets would receive a minimum five years of data exclusivity under the Drug Price Competition and Patent Term Restoration Act, also known as the Hatch-Waxman Act.

Before a new pharmaceutical product may be marketed in the United States, the FDA must approve an NDA, for a new drug. The steps required before the FDA will approve an NDA generally include non-clinical studies followed by multiple stages of clinical

trials conducted by the trial sponsor; sponsor submission of the NDA application to the FDA for review; the FDA's review of the data to assess the drug's safety and effectiveness; and the FDA's inspection of the facilities where the product will be manufactured.

As a condition of product approval, the FDA may require a sponsor to conduct post-marketing clinical trials, known as Phase 4 trials, and surveillance programs to monitor the effect of the approved product. The FDA may limit further marketing of a product based on the results of these post-market trials and programs. Any modifications to a drug, including new indications or changes to labeling or manufacturing processes or facilities, may require the submission and approval of a new or supplemental NDA before the modification can be implemented, which may require that we generate additional data or conduct additional non-clinical studies and clinical trials. Our ongoing manufacture and distribution of drugs is subject to continuing regulation by the FDA, including recordkeeping requirements, reporting of adverse experiences associated with the product, and adherence to current Good Manufacturing Practices, or cGMPs, which regulate all aspects of the manufacturing process. We are also subject to numerous regulatory requirements relating to the advertising and promotion of drugs, including, but not limited to, standards and regulations for direct-to-consumer advertising. Failure to comply with the applicable regulatory requirements governing the manufacture and marketing of our products may subject us to administrative or judicial sanctions, including warning letters, product recalls or seizures, injunctions, fines, civil penalties and/or criminal prosecution.

Sales and Marketing. The marketing practices of U.S. pharmaceutical companies are generally subject to various federal and state healthcare laws that are intended to prevent fraud and abuse in the healthcare industry and protect the integrity of government healthcare programs. These laws include anti-kickback laws and false claims laws. Anti-kickback laws generally prohibit a biopharmaceutical or medical device company from soliciting, offering, receiving or paying any remuneration to generate business, including the purchase or prescription of a particular product. False claims laws generally prohibit anyone from knowingly and willingly presenting, or causing to be presented, any claims for payment for reimbursed drugs or services to third-party payors (including Medicare and Medicaid) that are false or fraudulent. Although the specific provisions of these laws vary, their scope is generally broad and there may not be regulations, guidance or court decisions that apply the laws to any particular industry practices, including the marketing practices of pharmaceutical and medical device companies. Violations of fraud and abuse laws may be punishable by criminal or civil sanctions and/or exclusion from federal healthcare programs (including Medicare and Medicaid). The U.S. federal government and various states have also enacted laws to regulate the sales and marketing practices of pharmaceutical or medical device companies. These laws and regulations generally limit financial interactions between manufacturers and healthcare providers; require disclosure to the federal or state government and public of such interactions; and/or require the adoption of compliance standards or programs. Many of these laws and regulations contain ambiguous requirements or require administrative guidance for implementation. Given the lack of clarity in laws and their implementation, our activities could be subject to penalties under the pertinent laws and regulations.

Healthcare Reform. The United States and state governments continue to propose and pass legislation designed to regulate the healthcare industry. The ACA included changes that significantly affected the pharmaceutical industry, such as:

- Increasing drug rebates paid to state Medicaid programs under the Medicaid Drug Rebate Program for brand name and generic prescription drugs and extending those rebates to Medicaid managed care;
- Requiring pharmaceutical manufacturers to provide discounts on brand name prescription drugs sold to Medicare beneficiaries whose prescription drug costs cause the beneficiaries to be subject to the Medicare Part D coverage gap; and
- Imposing an annual fee on manufacturers and importers of brand name prescription drugs reimbursed under certain government programs, including Medicare and Medicaid.

The ACA includes provisions designed to increase the number of Americans covered by health insurance. Specifically, since 2014, the ACA has required most individuals to maintain health insurance coverage or potentially to pay a penalty for noncompliance and has offered states the option of expanding Medicaid coverage to additional individuals. Additionally, policy efforts designed specifically to reduce patient out-of-pocket costs for medicines could result in new mandatory rebates and discounts or other pricing restrictions. Adoption of other new legislation at the federal or state level could further affect demand for, or pricing of, our products.

Anti-Corruption. The Foreign Corrupt Practices Act of 1977, as amended, or FCPA, prohibits U.S. corporations and their representatives from offering, promising, authorizing or making payments to any foreign government official, government staff member, political party or political candidate in an attempt to obtain or retain business abroad. The scope of the FCPA includes interactions with certain healthcare professionals in many countries. Other countries have enacted similar anti-corruption laws and/or regulations. Individual states, acting through their attorneys general, have sought to regulate the marketing of prescription drugs under state consumer protection and false advertising laws.

Pricing and Reimbursement. Pricing for our pharmaceutical products will depend in part on government regulation. We will likely be required to offer discounted pricing or rebates on purchases of pharmaceutical products under various federal and state healthcare programs, such as the Medicaid Drug Rebate Program, the "federal ceiling price" drug pricing program, the 340B drug pricing program and the Medicare Part D Program. We will also be required to report specific prices to government agencies under healthcare programs, such as the Medicaid Drug Rebate Program and Medicare Part B. The calculations necessary to determine the prices reported are complex and the failure to report prices accurately may expose us to penalties.

In the United States, Medicaid currently covers all smoking cessation products including varenicline and bupropion. In March 2010, the Patient Protection and Affordable Care Act, or ACA, as amended by the Healthcare and Education Reconciliation Act, or collectively, the Healthcare Reform Law, was passed, which substantially changes the way healthcare is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry. Section 2502 of the ACA specifies that tobacco cessation medications will be removed from the list of optional medications and required for inclusion in states' prescription drug benefit. On May 2, 2014 the Department of Health and Human Services, or HHS, provided guidance into insurance coverage policy that health plans would be in compliance if they cover, among other items, screening for tobacco use, individual, group and phone counseling, all FDA approved tobacco cessation medications (both prescription and OTC) when prescribed by a healthcare provider, at least two quit attempts per year, four sessions of counseling and 90 days of treatment, with no cost sharing (co-pay) required.

Government and private third-party payers routinely seek to manage utilization and control the costs of our products. For example, the majority of states use preferred drug lists to restrict access to certain pharmaceutical products under Medicaid. Given certain states' current and potential ongoing fiscal crises, a growing number of states are considering a variety of cost-control strategies, including capitated managed care plans that typically contain cost by restricting access to certain treatments.

Outside the United States

We expect to encounter similar regulatory and legislative issues in most other countries in which we seek to develop and commercialize cytisinicline.

New Drug Approvals and Pharmacovigilance. In the EU, the approval of new drugs may be achieved using the Mutual Recognition Procedure, the Decentralized Procedure or the EU Centralized Procedure. These procedures apply in the EU member states, plus the EEA countries, Norway, Iceland and Liechtenstein. The use of these procedures generally provides a more rapid and consistent approval process across the EU and EEA than was the case when the approval processes were operating independently within each country.

In 2012, new pharmacovigilance legislation came into force in the EU. Key changes included the establishment of a new Pharmacovigilance Risk Assessment Committee within the EMA, with responsibility for reviewing and making recommendations on product safety issues for the EU authorities. It also introduced the possibility for regulators to require pharmaceutical companies to conduct post-authorization efficacy studies at the time of approval, or at any time afterwards in light of scientific developments. There are also additional requirements regarding adverse drug reaction reporting and additional monitoring of products. Outside developed markets such as the EU and Japan, pharmacovigilance requirements vary and are typically less extensive.

The U.K. ceased to be a member state of the EU on January 31, 2020 (commonly known as Brexit). Since a significant portion of the regulatory framework in the U.K. is derived from the regulations of the EU, Brexit could materially change the regulatory framework applicable to the approval of our product candidates and other aspects of our business in the U.K., such as the pricing and importation of prescription products. It remains to be seen how Brexit will impact regulatory requirements for product candidates and products in the U.K. in the long term. The Medicines and Healthcare Products Regulatory Agency, or MHRA, has recently published detailed guidance for industry and organizations to follow now the transition period is over, which will be updated as the U.K.'s regulatory position on medicinal products and medical devices evolves over time. Brexit has also created uncertainty with regard to data protection regulation in the U.K., and in particular, how data transfers from the EU to the U.K. will be regulated. The EU and the U.K. have agreed a bridging period of up to six months to allow the continued free flow of data from the EU to the U.K., during which time the European Commission will assess whether the U.K. will be granted adequacy status. There is no certainty that an adequacy decision will be granted. If it is not, legal uncertainties regarding the flow of data across borders could increase the complexity and cost of transferring personal data from the EU to the U.K.

Health authorities in many middle- and lower-income countries require marketing approval by a recognized regulatory authority (i.e., similar to the authority of the FDA or the EMA) before they begin to conduct their application review process and/or issue their final approval. Many authorities also require local clinical data in the country's population in order to receive final marketing approval. These requirements delay marketing authorization in those countries relative to the United States and Europe.

CONTRACT RESEARCH AGREEMENTS

Our strategy is to outsource certain product development activities and have established contract research agreements for, non-clinical, clinical, manufacturing and some data management services. We choose which business or institution to use for these services based on their expertise, capacity and reputation and the cost of the service.

We also provide or have provided quantities of our product candidates to academic research institutions to investigate the mechanism of action and evaluate novel combinations of product candidates with other cancer therapies in various cancer indications. These collaborations expand our research activities for our product candidates with modest contribution from us.

MANUFACTURING

We do not own or operate manufacturing facilities for the production of cytisinicline, though we may develop our own manufacturing operations in the future. We currently depend on Sopharma as supplier and contract manufacturer for all of our required raw materials, active pharmaceutical ingredients and finished drug product for our clinical trials. In addition to our Sopharma relationship, we utilize contract manufacturing organizations for the clinical packaging supplies of cytisinicline. We currently employ internal resources and third-party consultants to manage our clinical manufacturing activities.

Sopharma sources cytisinicline from the *Laburnum anagyroides* plant, a shrub or small tree native to, and widely distributed throughout, Bulgaria, south Central Europe and the northwestern Balkan Peninsula. The seed pods are harvested from the shrubs and dried. Each tree takes approximately four to six years to reach maturity for harvesting and has a productive life expectancy of 20 to 25 years. Seeds are harvested annually, dried and stored for processing into cytisinicline. *Laburnum anagyroide* seeds in their natural state are highly toxic and the extraction process removes the toxins to produce highly purified cytisinicline. Sopharma controls a number of Laburnum orchards throughout Bulgaria in addition to sourcing seeds and cytisinicline starting material from certain third-party suppliers. We expect Sopharma to continue stockpiling *cytisinicline* to meet the projected demand from us upon commercial launch.

The active pharmaceutical ingredient, or API, manufacturing process utilizes a series of techniques including milling, solvent extraction, filtration and purification. Critical control steps and manufacturing intermediates have been identified and are controlled by internally developed specifications and methods to ensure a consistent and reproducible process. The highly purified cytisinicline is dried, sieved and packed for storage until further processing into drug product. The cytisinicline API manufacturing process has been developed and refined over many years of manufacture by Sopharma, which has significant expertise in manufacturing cytisinicline.

Sopharma manufactures cytisinicline API in its facilities in Bulgaria, which are near the capital, Sofia. The API processing facility complies with EU cGMP requirements and has been inspected by the Bulgarian Drug Agency. Sopharma is in the process of building a new API facility specifically for cytisinicline within its tableting plant in Sofia.

Raw materials are essential to our business and are normally available in quantities adequate to meet the needs of our business. Where there are exceptions, the temporary unavailability of those raw materials has not historically had a material adverse effect on our financial results; however, uncertainties in supply chain, transportation logistics and costs, and political and economic conditions could result in disruptions in our operations and materially impact our financial results.

SALES AND MARKETING

Our commercial strategy may include the use of strategic partners, distributors, a contract sale force or the establishment of our own commercial and specialty sales force. We plan to further evaluate these alternatives including the potential to market and distribute direct to consumers via online channels leveraging telehealth solutions. We intend to seek partners in territories where we have no commercial experience and intend to directly market in niche markets where a small cost-effective commercial capability can generate direct revenues.

INTELLECTUAL PROPERTY

The U.S. Supreme Court has held that certain claims to naturally occurring substances are not patentable. Cytisinicline is a naturally occurring product and, therefore, the compound itself is not patentable in the United States. Furthermore, cytisinicline has been used in other parts of the world for decades, creating further challenges to patenting uses of the compound.

Our development and commercialization of cytisinicline is protected by our exclusive supply agreement with Sopharma and Sopharma’s proprietary technology, experience and expertise in cytisinicline extraction. In addition, we intend to utilize market

exclusivity laws including those under the Hatch-Waxman Act in the United States and exclusivity under Directive 2004/27/EC in the EU.

Additionally, we are actively building an intellectual property portfolio around our clinical-stage product candidate and research programs. A key component of this portfolio strategy is to seek international patent protection with patent applications in the United States and in major market countries that we consider important to the development of our business. As of December 31, 2021, we own a portfolio of four patent families. Those families cover cytisinicline derivatives (being prosecuted in the United States, Australia, Canada, China, Europe, U.K. and Japan), novel cytisinicline salts (being prosecuted in the United States, Australia, Canada, China, Europe, Hong Kong, South Korea, Japan and New Zealand with issued patents in the U.K., Canada, United States, Mexico and South Africa), and novel cytisinicline dosing methods being prosecuted in the United States, Brazil, Canada, China, Europe, Japan, South Korea, Mexico, and New Zealand, with issued patents in the United States. Additionally, we have in-licensed rights from Sopharma to two patent families relating to a new method of cytisinicline extraction, as well as cytisinicline formulations. As of December 31, 2021, we owned or in-licensed 7 issued patents and 26 pending patent applications. These patents have expirations dates ranging from 2037 to 2040, absent any term adjustments or extensions.

Our success depends in part on our ability to obtain and maintain proprietary protection for our product candidates and other discoveries, inventions, trade secrets and know-how that are critical to our business operations. Our success also depends in part on our ability to operate without infringing the proprietary rights of others, and in part, on our ability to prevent others from infringing our proprietary rights. A comprehensive discussion on risks relating to intellectual property is provided under "Risk Factors—Risks Related to Our Intellectual Property."

In addition to patent protection, we rely on trade secrets, trademark protection and know-how to expand our proprietary position around our chemistry, technology and other discoveries and inventions that we consider important to our business. We also seek to protect our intellectual property in part by entering into confidentiality agreements with our employees, consultants, scientific advisors, clinical investigators and other contractors and also by requiring our employees, commercial contractors and certain consultants and investigators, to enter into invention assignment agreements that grant us ownership of any discoveries or inventions made by them.

COMPETITION

The development and commercialization of new products is highly competitive. We face competition from major pharmaceutical companies, specialty pharmaceutical companies, biotechnology companies, universities and other research institutions worldwide with respect to smoking cessation and other product candidates that it may seek to develop or commercialize in the future. We are aware that many companies have therapeutics marketed or in development for smoking cessation, including, Pfizer Inc., GlaxoSmithKline Plc, Merck & Co., Novartis, Novo Nordisk, Johnson & Johnson, Invion, Embera Neurotherapeutics, Inc., 22nd Century Group, Inc., Quit4Good, zpharm, NAL Pharmaceuticals, Selecta Biosciences, Omeros, Aradigm, Adamed, Aflofarm, Axsome, Amygdala, Smoke Free Therapeutics, Antidote Therapeutics, Currax, NFL Biosciences, Palisades Therapeutics, Ro and others. We expect that our competitors and potential competitors have historically dedicated, and will continue to dedicate, significant resources to aggressively develop and commercialize their products in order to take advantage of the significant market opportunity.

Prescription and Over-the-Counter Treatments

Two oral prescription drugs for smoking cessation are currently available in the United States, Chantix and Zyban, and their generic equivalents, varenicline and bupropion, respectively. Both have been proven effective in aiding smoking cessation, however, each is associated with a number of adverse effects.

In June 2021, Pfizer Inc. halted the distribution of Chantix after heightened levels, above the FDA's acceptable daily intake limit, of nitrosamines were found in some lots of Chantix pills. In September 2021, Pfizer announced a nationwide recall in the United States of all lots of Chantix and have also withdrawn the product in other countries around the globe. Prior to market withdrawal and launch of generic Chantix (varenicline), global sales of branded Chantix peaked at $1.1 billion. Of those sales, approximately 75% were attributable to the U.S. market.

The most common OTC treatments bought in pharmacies for smoking cessation in the United States and worldwide are NRTs such as nicotine gums, nicotine lozenges, and nicotine patches. Each of these products delivers nicotine to the body although they generally do so at different rates and to different parts of the body than does a traditional cigarette. As concluded by the authors of several published clinical trials conducted by others, these therapies are generally less effective than prescription treatments. Recognized brands include Niquitin , Nicotinell , Nicorette and Nicoderm. Depending on the duration of treatment, the average cost of certain OTC smoking cessation treatments can exceed prescription treatments.

Pharmaceutical companies, including larger companies in the industry, who have extensive expertise in non-clinical and clinical testing and in obtaining regulatory approvals for products, may develop other OTC treatments for smoking cessation. In addition, academic institutions, government agencies and other public and private organizations conducting research may seek patent protection with respect to potentially competitive products or technologies. These organizations may also establish exclusive collaborative or licensing relationships with our competitors.

HUMAN CAPITAL RESOURCES

As of December 31, 2021, we had a total of 16 employees, of whom eight were engaged in research and development functions, including clinical development, regulatory affairs and manufacturing, and eight were engaged in general and administrative functions, including accounting and finance, administration, and corporate communications.

All of our employees have entered into non-disclosure agreements regarding our intellectual property, trade secrets and other confidential information. None of our employees are represented by a labor union or covered by a collective bargaining agreement, nor have we experienced any work stoppages. We believe that we maintain satisfactory relations with our employees.

From time to time, we also use outside consultants to provide advice on our clinical development plans, research programs, administration and potential acquisitions of new technologies.

We believe that our future success largely depends upon our continued ability to attract and retain highly skilled employees. We emphasize a number of measures and objectives in managing our human capital assets, including, among others, employee engagement, development, and training, talent acquisition and retention, employee safety and wellness, diversity and inclusion, and compensation and pay equity. We provide our employees with competitive salaries and bonuses, opportunities for equity ownership, development programs that enable continued learning and growth and a robust employment package that promotes well-being across all aspects of their lives, including health care, retirement planning and paid time off.

COMPANY INFORMATION

We were incorporated in California in October 1991 and subsequently reorganized as a Delaware corporation in March 1995. Our principal executive office is located at 1040 West Georgia Street, Suite 1030, Vancouver, B.C. V6E 4H1, Canada and our telephone number is (604) 210-2217.

AVAILABLE INFORMATION

We maintain a website at http://www.achievelifesciences.com. The information contained on or accessible through our website is not part of this Annual Report on Form 10-K. Our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, are available free of charge on our website as soon as reasonably practicable after we electronically file such reports with, or furnish those reports to, the SEC. The SEC also maintains an Internet site that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC at http://www.sec.gov.

ITEM 1A.

Summary of Risk Factors

An investment in our common stock involves various risks, and prospective investors are urged to carefully consider the matters discussed in the section titled “Risk Factors” prior to making an investment in our common stock. These risks include, but are not limited to, the following:

- We have incurred losses since inception, have a limited operating history on which to assess our business and anticipate that we will continue to incur losses for the foreseeable future.
- We expect that we will need additional funding before we can become profitable from any potential future sales of cytisinicline. If we fail to obtain additional financing when needed, we may be unable to complete the development, regulatory approval and commercialization of our product candidates.

- We have never generated any revenue from product sales and may never be profitable.
- We are dependent upon a single company for the manufacture and supply of cytisinicline.
- Cytisinicline is currently our sole product candidate and there is no guarantee that we will be able to successfully develop and commercialize cytisinicline.
- The development of our product candidate is dependent upon securing sufficient quantities of cytisinicline from trees and other plants, which grows outside of the United States in a limited number of locations.
- If we do not obtain the necessary regulatory approvals in the United States and/or other countries, we will not be able to sell cytisinicline.
- It is difficult to evaluate our current business, predict our future prospects and forecast our financial performance and growth.
- The ongoing COVID-19 pandemic has and may continue to adversely impact our business, including our non-clinical development activities and planned clinical trials.
- We expect to continue to rely on third parties to manufacture cytisinicline for use in clinical trials, and we intend to exclusively rely on Sopharma to produce and process cytisinicline, if approved, which may be impacted by the military conflict between Russia and Ukraine, including the possibility of expanded regional or global conflict and related economic sanctions.
- Our commercialization of cytisinicline could be stopped, delayed or made less profitable if Sopharma fails to obtain approval of government regulators, fails to provide us with sufficient quantities of product, or fails to do so at acceptable quality levels or prices.
- Sopharma may breach its supply agreement with us and sell cytisinicline into our territories or permit third parties to export cytisinicline into our territories and negatively affect our commercialization efforts of our products in our territories.
- We face substantial competition, and our competitors may discover, develop or commercialize products faster or more successfully than us.
- We may not be successful in obtaining or maintaining necessary rights to cytisinicline, product compounds and processes for our development pipeline through acquisitions and in-licenses.

RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the risks and uncertainties described below, together with all of the other information contained in this Annual Report on Form 10-K and in the other periodic and current reports and other documents we file with the Securities and Exchange Commission, before deciding to invest in our common stock. If any of the following risks materialize, our business, financial condition, results of operation and future prospects will likely be materially and adversely affected. In that event, the market price of our common stock could decline, and you could lose all or part of your investment. This list is not exhaustive, and the order of presentation does not reflect management's determination of priority or likelihood.

Risks Related to Our Financial Condition and Capital Requirements

We have incurred losses since inception, have a limited operating history on which to assess our business and anticipate that we will continue to incur losses for the foreseeable future.

We are a clinical development-stage specialty pharmaceutical company with a limited operating history, are not profitable, have incurred losses in each year since our inception and expect to continue incurring losses for the foreseeable future.

Pharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. We have devoted substantially all of our financial resources to identify, acquire, and develop cytisinicline, including providing general and administrative support for our operations. To date, we have financed our operations primarily through the sale of equity securities and convertible promissory notes. The amount of our future net losses will depend, in part, on the rate of our future expenditures and our ability to obtain funding through equity or debt financings, strategic collaborations, or grants.

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

- continue the clinical development of cytisinicline;
- advance cytisinicline development into larger, more expensive clinical trials;
- initiate additional non-clinical, clinical, or other trials or studies for cytisinicline;
- seek to attract and retain skilled personnel;
- undertake the manufacturing of cytisinicline or increase volumes manufactured by third parties;
- seek regulatory and marketing approvals and reimbursement for cytisinicline;
- make milestone, royalty or other payments under third-party license and/or supply agreements;
- establish a sales, marketing, and distribution infrastructure to commercialize any product for which we may obtain marketing approval and market for ourselves;
- seek to discover, identify, assess, acquire, and/or develop other product candidates;
- seek to establish, maintain, protect, and expand our intellectual property portfolio; and
- experience any delays or encounter issues with the development and potential for regulatory approval of cytisinicline such as safety issues, clinical trial accrual delays, longer follow-up for planned studies, additional major studies, or supportive studies necessary to support marketing approval.

Further, the net losses we incur may fluctuate significantly from quarter to quarter and year to year, such that a period-to-period comparison of our results of operations may not be a good indication of our future performance.

We expect that we will need additional funding before we can become profitable from any potential future sales ofytisinicline. If we fail to obtain additional financing when needed, we may be unable to complete the development, regulatory approval and commercialization of our product candidates.

We have expended and continue to expend substantial funds in connection with our product development activities and clinical trials and regulatory approvals. In addition, we expect to incur significant expenses and increasing operating losses for at least the next several years as we continue our clinical development of, and seek regulatory approval for, cytisinicline and add personnel necessary to operate as a public company with an advanced clinical candidate. We expect that our operating losses will fluctuate significantly from quarter to quarter and year to year due to timing of clinical development programs and efforts to achieve regulatory approval.

Funds generated from our operations will be insufficient to enable us to bring all of our products currently under development to commercialization. Accordingly, we will need to raise substantial additional capital to continue to fund our operations from the sale of our securities, debt, partnering arrangements, non-dilutive fundraising or other financing transactions in order to finance the commercialization of our product candidate. The current financing environment in the United States, particularly for biotechnology companies like us, is exceptionally challenging and we can provide no assurances as to when such an environment will improve. Further, the uncertainty with respect to our operations and the market generally due to the COVID-19 pandemic may also make it challenging to raise additional capital on favorable terms, if at all. For these reasons, among others, we cannot be certain that additional financing will be available when and as needed or, if available, that it will be available on acceptable terms. If financing is available, it may be on terms that adversely affect the interests of our existing stockholders. If adequate financing is not available, we may need to continue to reduce or eliminate our expenditures for research and development of cytisinicline, and may be required to suspend development of cytisinicline. Our actual capital requirements will depend on numerous factors, including:

- our commercialization activities and arrangements;
- the progress and results of our research and development programs;
- the progress of our non-clinical and clinical testing;
- the time and cost involved in obtaining regulatory approvals for our product candidate;
- the cost of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights with respect to our intellectual property;
- the effect of competing technological and market developments;
- the effect of changes and developments in our existing collaborative, licensing and other relationships;
- the effect of interest rate increases, which may increase the cost of our borrowing under our loan facility, which includes an adjustable-rate component; and
- the terms of any new collaborative, licensing, commercialization and other arrangements that we may establish.

We may not be able to secure sufficient financing on acceptable terms, or at all. Without additional funds, we may be forced to delay, scale back or eliminate some of our research and development activities or other operations and potentially delay product development in an effort to provide sufficient funds to continue our operations. If any of these events occur, our ability to achieve our development and commercialization goals would be adversely affected.

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

We have no products approved for commercialization and have never generated any revenue from product sales. Our ability to generate revenue and achieve profitability depends on our ability, alone or with strategic collaborators, to successfully complete the development of, and obtain the regulatory and marketing approvals necessary to commercialize cytisinicline. We do not anticipate generating revenue from product sales for the foreseeable future. Our ability to generate future revenue from product sales depends heavily on our success in many areas, including but not limited to:

- completing research and development of cytisinicline;
- obtaining regulatory and marketing approvals for cytisinicline;

- manufacturing product and establishing and maintaining supply and manufacturing relationships with third parties that are commercially feasible, satisfy regulatory requirements and meet our supply needs in sufficient quantities to satisfy market demand for cytisinicline, if approved;
- marketing, launching and commercializing any product for which we obtain regulatory and marketing approval, either directly or with a collaborator or distributor;
- obtaining reimbursement or pricing for cytisinicline that supports profitability;
- gaining market acceptance of cytisinicline as a treatment option;
- addressing any competing products, including the potential for generic cytisinicline products;
- protecting and enforcing our intellectual property rights, if any, including patents, trade secrets, and know-how;
- negotiating favorable terms in any collaboration, licensing, commercialization, or other arrangements into which we may enter; and
- attracting, hiring, and retaining qualified personnel.

Even if a product candidate that we develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing that candidate. Additionally, if we are not able to generate sufficient revenue from the sale of any approved products to cover our operating costs, we may never become profitable. If we obtain regulatory approval to market a product candidate, our future revenue will depend upon the size of any markets in which our product candidate may receive approval, and our ability to achieve sufficient market acceptance, pricing, reimbursement from third-party payors, and adequate market share for our product candidate in those markets.

We are dependent upon a single company for the manufacture and supply of cytisinicline.

Our single product candidate, cytisinicline, has been in-licensed from a third party. We are required to continue to contract with Sopharma AD, or Sopharma, to continue our development of, and potential commercialization of, cytisinicline pursuant to a supply agreement with Sopharma. Sopharma currently manufactures all of its cytisinicline API in its facilities in Bulgaria. The conflict in Ukraine, including the possibility of expanded regional or global conflict and related economic sanctions, may have negative impacts on Sopharma's business, which could cause them to reduce or terminate investments in the cytisincline program. If the supply agreement with Sopharma is terminated, we will need to develop or acquire alternative supply and manufacturing capabilities for cytisinicline, which we may not be able to do on commercially viable terms or at all.

Risks Related to the Development of Our Product Candidate Cytisinicline

Cytisinicline is currently our sole product candidate and there is no guarantee that we will be able to successfully develop and commercialize cytisinicline.

We are currently dependent on the potential development of a single product candidate, cytisinicline. We are still developing our sole product candidate, and cytisinicline cannot be marketed or sold in the United States or in foreign markets until regulatory approval has been obtained from the FDA or applicable foreign regulatory agencies. The process of obtaining regulatory approval is expensive and time consuming. The FDA and foreign regulatory authorities may never approve cytisinicline for sale and marketing, and even if cytisinicline is ultimately approved, regulatory approval may be delayed or limited in the United States or in other jurisdictions. Even if we are authorized to sell and market cytisinicline in one or more markets, there is no assurance that we will be able to successfully market cytisinicline or that cytisinicline will achieve market acceptance sufficient to generate profits. If we are unable to successfully develop and commercialize cytisinicline due to failure to obtain regulatory approval for cytisinicline, to successfully market cytisinicline, to generate profits from the sale of cytisinicline, or due to other risk factors outlined in this report, it would have material adverse effects on our business, financial condition, and results of operations as cytisinicline is currently our sole product candidate.

Results of earlier clinical trials of cytisinicline are not necessarily predictive of future results, and any advances of cytisinicline into clinical trials may not have favorable results or receive regulatory approval.

Even if our clinical trials are completed as planned, we cannot be certain that their results will be consistent with the results of the earlier clinical trials of cytisinicline. Positive results in non-clinical testing and past clinical trials with respect to the safety and efficacy of cytisinicline do not ensure that results from subsequent clinical trials will also be positive, and we cannot be sure that the results of subsequent clinical trials will replicate the results of prior clinical trials and non-clinical testing. Any such failure may cause us to abandon cytisinicline, which would negatively affect our ability to generate any product revenues.

Clinical trials are costly, time consuming and inherently risky, and we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities.

Clinical development is expensive, time consuming and involves significant risk. We cannot guarantee that any clinical trial will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical trials can occur at any stage of development. Events that may prevent successful or timely completion of clinical development include, but are not limited to:

- delays in reaching agreement on acceptable terms with clinical research organizations, or CROs, and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and clinical trial sites;
- delays in obtaining required institutional review board, or IRB, approval at each clinical trial site;
- failure to permit the conduct of a clinical trial by regulatory authorities, after review of an investigational new drug or equivalent foreign application or amendment;
- delays in recruiting qualified patients in its clinical trials;
- failure by clinical sites, CROs or other third parties to adhere to clinical trial requirements;
- failure by clinical sites, CROs or other third parties to perform in accordance with the good clinical practices requirements of the FDA or applicable foreign regulatory guidelines;
- disruptions to our supply chain for the cytisinicline required for our clinical trials;
- patients terminating enrollment in our clinical trials;
- failure by clinical sites, CROs or other third parties to continue to conduct research and development due to adverse impacts of the COVID-19 pandemic;
- adverse events or tolerability issues significant enough for the FDA or other regulatory agencies to put any or all clinical trials on hold;
- inability to generate satisfactory non-clinical, toxicology, or other in vivo or in vitro data or diagnostics to support the initiation or continuation of clinical trials;
- animal toxicology issues significant enough for the FDA or other regulatory agencies to disallow investigation in humans;
- occurrence of adverse events associated with our product candidate;
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols;
- the cost of clinical trials of cytisinicline;
- negative or inconclusive results from our clinical trials which may result in us deciding, or regulators requiring us, to conduct additional clinical trials or abandon development programs in ongoing or other planned indications for cytisinicline;
- discovery of impurities in our cytisinicline drug product, such as nitrosamines, above the regulators' prescribed thresholds; and
- delays in the manufacture or packaging of sufficient quantities of cytisinicline for use in clinical trials

Any inability to successfully complete clinical development and obtain regulatory approval for cytisinicline could result in additional costs to us or impair our ability to generate revenue. In addition, if we make manufacturing or formulation changes to cytisinicline, we may need to conduct additional non-clinical trials or the results obtained from such new formulation may not be consistent with previous results obtained. Clinical trial delays could also shorten any periods during which our products have patent protection and may allow competitors to develop and bring products to market before we do, which could impair our ability to successfully commercialize cytisinicline and may harm our business and results of operations.

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

Undesirable side effects caused by cytisinicline could cause us or regulatory authorities to interrupt, delay, or terminate clinical trials or even if approved, result in a restrictive label or delay regulatory approval by the FDA or comparable foreign authorities.

Additionally, even if cytisinicline receives marketing approval, and we or others later identify undesirable side effects caused by cytisinicline, potentially significant negative consequences could result, including but not limited to:

- regulatory authorities may withdraw approvals of cytisinicline;
- regulatory authorities may require additional warnings on the cytisinicline label;
- we may be required to create a Risk Evaluation and Mitigation Strategy, or REMS, plan, which could include a medication guide outlining the risks of such side effects for distribution to patients, a communication plan for healthcare providers, and/or other elements to assure safe use;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

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

The development of our product candidate is dependent upon securing sufficient quantities of cytisinicline from trees and other plants, which grows outside of the United States in a limited number of locations.

The therapeutic component of our product candidate, cytisinicline, is derived from the seeds of the *Laburnum anagyroides trees and other* plants, which grows in the mountains of Southern Europe and other limited locations around the world. We currently secure cytisinicline exclusively from Sopharma, a Bulgarian third-party supplier. Our current supply agreement with Sopharma expires on July 28, 2037, unless extended by mutual agreement of us and Sopharma. There can be no assurances that *Laburnum anagyroides trees and other* plants will continue to grow in sufficient quantities to meet commercial supply requirements or that the countries from which we can secure *them* will continue to allow the exportation of cytisinicline. For example, *Laburnum anagyroides* trees take approximately four to six years to reach maturity for harvesting and have a productive life expectancy of 20 to 25 years. There is no guarantee that Sopharma will plant sufficient trees or secure sufficient quantities of cytisinicline drug product to manage supply for our markets or to meet our forecasts. Additionally, economic or political instability or disruptions, such as the conflict in Ukraine, could negatively affect our supply chain or increase our costs. If these types of events or disruptions continue to occur, they could have a material adverse effect on our business, financial condition, results of operations and cash flows. In the event we are no longer able to obtain cytisinicline from Sopharma, or in sufficient quantities, we may not be able to produce our proposed products and our business will be adversely affected.

Our product development program may not uncover all possible adverse events that patients who take cytisinicline or our other product candidates may experience. The number of subjects exposed to cytisinicline or our other product candidates and the average exposure time in the clinical development program may be inadequate to detect rare adverse events, or chance findings, that may only be detected once the product is administered to more patients and for greater periods of time.

Clinical trials by their nature utilize a sample of the potential patient population. We cannot be fully assured that rare and severe side effects of cytisinicline will be uncovered. Such rare and severe side effects may only be uncovered with a significantly larger number of patients exposed to cytisinicline or over a significantly longer period of time. If such safety problems occur or are identified after cytisinicline reaches the market in the United States, or if such safety problems occur or are identified in foreign markets where cytisinicline is currently marketed, the FDA may require that we amend the labeling of cytisinicline or recall it, or may even withdraw approval for cytisinicline.

If the use or misuse of cytisinicline harms patients, or is perceived to harm patients even when such harm is unrelated to cytisinicline, our regulatory approvals, if any, could be revoked or otherwise negatively impacted and we could be subject to costly and damaging product liability claims. If we are unable to obtain adequate insurance or are required to pay for liabilities resulting from a claim excluded from, or beyond the limits of, our insurance coverage, a material liability claim could adversely affect our financial condition.

The use or misuse of cytisinicline in clinical trials and the sale of cytisinicline if marketing approval is obtained, exposes us to the risk of potential product liability claims. Product liability claims might be brought against us by consumers, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our product. There is a risk that cytisinicline may induce adverse events. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, during the course of treatment, patients may suffer adverse events for reasons that may be related to cytisinicline. Such

events could subject us to costly litigation, require us to pay substantial amounts of money to injured patients, delay, negatively impact or end our opportunity to receive or maintain regulatory approval to market cytisinicline, if any, or require us to suspend or abandon our commercialization efforts. Even in a circumstance in which an adverse event is unrelated to cytisinicline, an investigation into such circumstance may be time-consuming or inconclusive. Such investigations may delay our regulatory approval process or impact and limit the type of regulatory approvals cytisinicline receives or maintains. As a result, a product liability claim, even if successfully defended, could have a material adverse effect on our business, financial condition or results of operations.

If we obtain marketing approval for cytisinicline, we will need to expand our insurance coverage to include the sale of commercial products. We cannot know if we will be able to continue to obtain product liability coverage and obtain expanded coverage if we require it, in sufficient amounts to protect us against losses due to liability, on acceptable terms, or at all. We may not have sufficient resources to pay for any liabilities resulting from a claim excluded from, or beyond the limits of, our insurance coverage.

Where we have provided indemnities in favor of third parties under our agreements with them, there is a risk that these third parties could incur liability and bring a claim under such indemnities. An individual may also bring a product liability claim against us alleging that cytisinicline causes, or is claimed to have caused, an injury or is found to be unsuitable for consumer use. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability, and a breach of warranties. Claims could also be asserted under state consumer protection acts. Any product liability claim brought against us, with or without merit, could result in:

- withdrawal of clinical trial volunteers, investigators, patients or trial sites or limitations on approved indications;
- an inability to commercialize, or if commercialized, a decreased demand for, cytisinicline;
- if commercialized, product recalls, withdrawals of labeling, marketing or promotional restrictions or the need for product modification;
- initiation of investigations by regulators;
- loss of revenue, if any;
- substantial costs of litigation, including monetary awards to patients or other claimants;
- liabilities that substantially exceed our product liability insurance, which we would then be required to pay ourselves;
- increased product liability insurance rates, or inability to maintain insurance coverage in the future on acceptable terms, if at all;
- diversion of management's attention from our business; and
- damage to our reputation and the reputation of our products and our technology.

Product liability claims may subject us to the foregoing and other risks, which could have a material adverse effect on our business, financial condition or results of operations.

Our business may be negatively affected by weather conditions, natural disasters, and the availability of natural resources, as well as by climate change.

In recent years, extreme weather events and changing weather patterns such as storms, flooding, drought, and temperature changes appear to have become more common. The production of cytisinicline from the *Laburnum anagyroides* and other plant depends on the availability of natural resources, including sufficient rainfall. Our exclusive supplier of cytisinicline, Sopharma, could be adversely affected if it experiences a shortage of fresh water due to droughts or if it experiences other adverse weather conditions. The long-term effects of climate change on general economic conditions and the pharmaceutical industry in particular are unclear and may heighten or intensify existing risk of natural disasters. As a result of such events, we could experience cytisinicline shortages from Sopharma, which could have a material adverse effect on our business, financial condition and results of operations.

In addition, the manufacturing and other operations of Sopharma are located near earthquake fault lines in Sofia, Bulgaria. In the event of a major earthquake, we could experience business interruptions from the disruption of our cytisinicline supplies, which could have a material adverse effect on our business, financial condition and results of operations.

We may conduct clinical trials internationally, which may trigger additional risks.

If we decide to conduct clinical trials in Europe or other countries outside of the United States, we will have additional regulatory requirements that we will have to meet in connection with our manufacturing, distribution, use of data and other matters. Failure to meet such regulatory requirements could delay our clinical trials, the approval, if any, of cytisinicline by the FDA or other regulatory authorities, or the commercialization of cytisinicline, or result in higher costs or deprive us of potential product revenues.

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

Because we have limited financial and human resources, we may forego or delay pursuit of opportunities with some programs or product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or more profitable market opportunities. Our spending on current and future research and development programs and future product candidates for specific indications may not yield any commercially viable products. We may also enter into additional strategic collaboration agreements to develop and commercialize some of our programs and potential product candidates in indications with potentially large commercial markets. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaborations, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate, or we may allocate internal resources to a product candidate in a therapeutic area in which it would have been more advantageous to enter into a partnering arrangement.

Risks Related to Regulatory Approval of Cytisinicline and Other Legal Compliance Matters

If we do not obtain the necessary regulatory approvals in the United States and/or other countries, we will not be able to sell cytisinicline.

We will need approval from the FDA to commercialize cytisinicline in the United States and approvals from similar regulatory authorities in foreign jurisdictions to commercialize cytisinicline in those jurisdictions. In order to obtain FDA approval of cytisinicline, we must submit an NDA to the FDA, demonstrating that cytisinicline is safe, pure and potent, and effective for its intended use. This demonstration requires significant research including completion of clinical trials. Satisfaction of the FDA's regulatory requirements typically takes many years, depending upon the type, complexity and novelty of the product candidate and requires substantial resources for research, development and testing. We cannot predict whether our clinical trials will demonstrate the safety and efficacy of cytisinicline or if the results of any clinical trials will be sufficient to advance to the next phase of development or for approval from the FDA. We also cannot predict whether our research and clinical approaches will result in data that the FDA considers safe and effective for the proposed indications of cytisinicline. The FDA has substantial discretion in the product approval process. The approval process may be delayed by changes in government regulation, future legislation or administrative action or changes in FDA policy that occur prior to or during our regulatory review. Even if we comply with all FDA requests, the FDA may ultimately reject one or more of our applications. We may never obtain regulatory approval for cytisinicline. Failure to obtain approval from the FDA or comparable regulatory authorities in foreign jurisdictions to commercialize cytisinicline will leave us without saleable products and therefore without any source of revenues. In addition, the FDA may require us to conduct additional clinical testing or to perform post-marketing studies, as a condition to granting marketing approval of a product or permit continued marketing, if previously approved. If conditional marketing approval is obtained, the results generated after approval could result in loss of marketing approval, changes in product labeling, and/or new or increased concerns about the side effects or efficacy of a product. The FDA has significant post-market authority, including the explicit authority to require post-market studies and clinical trials, labeling changes based on new safety information and compliance with FDA-approved risk evaluation and mitigation strategies. The FDA's exercise of its authority has in some cases resulted, and in the future could result, in delays or increased costs during product development, clinical trials and regulatory review, increased costs to comply with additional post-approval regulatory requirements and potential restrictions on sales of approved products. In foreign jurisdictions, the regulatory approval processes generally include the same or similar risks as those associated with the FDA approval procedures described above. We cannot be certain that we will receive the approvals necessary to commercialize cytisinicline for sale either within or outside the United States.

Even if we obtain regulatory approval for cytisinicline, we will remain subject to ongoing regulatory requirements in connection with the sale and distribution of cytisinicline.

Even if cytisinicline is approved by the FDA or comparable foreign regulatory authorities, we will be subject to ongoing regulatory requirements with respect to manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping, conduct of post-marketing clinical trials, and submission of safety, efficacy and other post-approval information, including both federal and state requirements in the United States and the requirements of comparable foreign regulatory authorities. Compliance with such regulatory requirements will likely be costly and the failure to comply would likely result in penalties, up to and including, the loss of such approvals from the FDA or comparable foreign regulatory authorities.

Manufacturers and manufacturers' facilities are required to continuously comply with FDA and comparable foreign regulatory authority requirements, including ensuring that quality control and manufacturing procedures conform to current cGMP regulations and corresponding foreign regulatory manufacturing requirements. As such, we, Sopharma and other contract manufacturers, if any, will be subject to continual review and inspections to assess compliance with cGMP and adherence to commitments made in any NDA or marketing authorization application.

Ongoing post-approval monitoring and clinical trial obligations may be costly to us and the failure to meet such obligations may result in the withdrawal of such approvals.

Any regulatory approvals that we receive for cytisinicline, if any, may be subject to limitations on the approved indicated uses for which cytisinicline may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials, and surveillance to monitor the safety and efficacy of cytisinicline. We will be required to report adverse reactions and production problems, if any, to the FDA and comparable foreign regulatory authorities. Any new legislation addressing product safety issues could result in delays in product development or commercialization, or increased costs to assure compliance. If our original marketing approval for cytisinicline was obtained through an accelerated approval pathway, we could be required to conduct a successful post-marketing clinical trial in order to confirm the clinical benefit for our products. An unsuccessful post-marketing clinical trial or failure to complete such a trial could result in the withdrawal of marketing approval.

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

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

Any government investigation of alleged violations of law would be expected to require us to expend significant time and resources in response and could generate adverse publicity. Any failure to comply with ongoing regulatory requirements may significantly and adversely affect our ability to develop and commercialize our products and the value of us and our operating results would be adversely affected.

We may be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws, and health information privacy and security laws. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

If we obtain FDA approval for cytisinicline and begin commercializing it in the United States, our operations may be subject to various federal and state fraud and abuse laws, including, without limitation, the federal Anti-Kickback Statute, the federal False Claims Act, and physician sunshine laws and regulations. These laws may impact, among other things, our proposed sales, marketing, and education programs. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce, or in return for, the purchase or recommendation of an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs;

- federal civil and criminal false claims laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payors that are false or fraudulent;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology and Clinical Health Act, and its implementing regulations, which imposes specified requirements relating to the privacy, security, and transmission of individually identifiable health information;

- the federal physician sunshine requirements under the Healthcare Reform Law requires manufacturers of products, devices, biologics, and medical supplies to report annually to the U.S. Department of Health and Human Services information related to payments and other transfers of value to physicians, other healthcare providers, and teaching hospitals, and ownership and investment interests held by physicians and other healthcare providers and their immediate family members and applicable group purchasing organizations; and

- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws that may apply to items or services reimbursed by any third-party payor, including governmental and private payors, to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require product manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures, and state laws governing the privacy and security of health information in specified circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. In addition, recent healthcare reform legislation has strengthened these laws. For example, the Healthcare Reform Law, among other things, amends the intent requirement of the federal anti-kickback and criminal healthcare fraud statutes. A person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it. Moreover, the Healthcare Reform Law provides that the government may assert that a claim including items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for purposes of the False Claims Act.

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

Healthcare legislative and executive reform measures may have a material adverse effect on our business, financialcondition or results of operations.

In the United States, there have been and continue to be a number of legislative initiatives to contain healthcare costs. For example, in March 2010, the Healthcare Reform Law was passed, which substantially changes the way healthcare is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry. The Healthcare Reform Law, among other things, addresses a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for products that are inhaled, infused, instilled, implanted, or injected, increases the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extends the rebate program to individuals enrolled in Medicaid managed care organizations, establishes annual fees and taxes on manufacturers of specified branded prescription products, and promotes a new Medicare Part D coverage gap discount program.

There have also been multiple recent U.S. congressional inquiries and proposed and adopted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs and biologics. In addition, Congress and multiple presidential administrations have indicated that they will continue to seek new legislative and/or administrative measures to control drug costs. We anticipate that additional state and federal healthcare measures could be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand or lower pricing for cytisinicline, or additional pricing pressures. Currently, the Healthcare Reform Law provides coverage for smoking cessation-related activities, including two counseling attempts for smoking cessation per year and medications for smoking cessation. If these provisions are repealed, in whole or in part, our business, financial condition, or results of operations could be negatively affected.

Further, the United Kingdom ceased to be a member state of the European Union on January 31, 2020 (commonly known as Brexit). Since a significant portion of the regulatory framework in the United Kingdom is derived from the regulations of the European Union, Brexit could materially change the regulatory framework applicable to the approval of cytisinicline, which could have a material adverse effect on us and our operations. Brexit may also result in other significant regulatory and legislative changes in the United Kingdom, which could, for example, affect the pricing of pharmaceutical products in the United Kingdom, which could in turn result in diminished performance for us. Even if the substance of regulatory changes resulting from Brexit does not have a significant impact on our operations, it is reasonable to expect that we would incur potentially significant costs in connection with complying with any new regulations.

Brexit may also have adverse effects on potential customers and collaborators of ours, which could indirectly have an adverse effect on us.

Our ability to obtain services, reimbursement or funding may be impacted by possible reductions in federal spending in the United States as well as globally.

U.S. federal government agencies currently face potentially significant spending reductions. Under the Budget Control Act of 2011, the failure of Congress to enact deficit reduction measures of at least $1.2 trillion for the years 2013 through 2021 triggered automatic cuts to most federal programs. These cuts would include aggregate reductions to Medicare payments to providers of up to two percent per fiscal year, which went into effect beginning on April 1, 2013 and will stay in effect through 2025 unless additional Congressional action is taken. The American Taxpayer Relief Act of 2012, which was enacted on January 1, 2013, among other things, reduced Medicare payments to several providers, including hospitals and imaging centers. The full impact on our business of these automatic cuts is uncertain.

If government spending is reduced, anticipated budgetary shortfalls may also impact the ability of relevant agencies, such as the FDA or the National Institutes of Health to continue to function at current levels. Amounts allocated to federal grants and contracts may be reduced or eliminated. These reductions may also impact the ability of relevant agencies to timely review and approve drug research and development, manufacturing, and marketing activities, which may delay our ability to develop, market and sell any products we may develop. Any reductions in government spending in countries outside the United States may also impact us negatively, such as by limiting the functioning of international regulatory agencies in countries outside the United States or by eliminating programs on which we may rely.

In July 2021, we announced that we were awarded a grant from the National Institute on Drug Abuse, or NIDA, of the National Institutes of Health, or NIH, to evaluate the use of cytisinicline as a treatment for cessation of nicotine e-cigarette use. This initial grant award, in the amount of $320,000, commenced on August 1, 2021, and is being utilized to complete critical regulatory and clinical operational activities, such as protocol finalization, clinical trial site identification, and submission of a new IND to the FDA for investigating cytisinicline in nicotine e-cigarette users. Upon completion of these milestones, as assessed by the NIH and subject to available funding, we expect to receive the next stage of the grant award of approximately $2.5 million, which will enable initiation of the Phase 2 ORCA-V1 clinical study evaluating cytisinicline in approximately 150 adult nicotine e-cigarette users in the United States.

The full grant award of $2.8 million is expected to cover approximately half of the ORCA-V1 clinical study costs. If amounts allocated to federal grants were reduced or eliminated, we would be required to fund the shortfall in the ORCA-V1 clinical study costs, which may result in delay of initiation of or cancellation of the study.

Our employees, independent contractors, consultants, commercial partners, principal investigators, or CROs 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.

We are exposed to the risk of fraud or misconduct by employees, independent contractors, consultants, commercial partners, principal investigators, or CROs, which could include intentional, reckless, negligent, or unintentional failures to comply with FDA regulations, comply with applicable fraud and abuse laws, provide accurate information to the FDA, report financial information or data accurately, or disclose unauthorized activities to us. This misconduct could also involve the improper use or misrepresentation of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter this type of misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, financial condition and results of operations, including the imposition of significant fines or other sanctions. Further, even if we are successful in asserting a defense, we may incur substantial costs in preparing and maintaining our defense and any such action would be time- and resource-intensive and potentially divert management's attention from the business, which could adversely affect our business and results of operations.

Risks Related to our Business Operations

It is difficult to evaluate our current business, predict our future prospects and forecast our financial performance and growth.

To date our business activities have been focused primarily on the development and regulatory approval of cytisinicline and its various alternative forms. Although we have not generated revenue to date, we expect that, after any regulatory approval, any receipt of revenue will be attributable to sales of cytisinicline, primarily in the United States, the European Union (including the United Kingdom) and Asia. Because we devote substantially all of our resources to the development of cytisinicline and rely on cytisinicline as our sole source of potential revenue for the foreseeable future, any factors that negatively impact this product, or result in decreasing product sales, would materially and adversely affect our business, financial condition and results of operations.

Our future success depends in part on our ability to attract, retain, and motivate other qualified personnel.

We will need to expand and effectively manage our managerial, operational, financial, development and other resources in order to successfully pursue our development and commercialization efforts for our existing and future product candidates. We expect to need additional scientific, technical, operational, financial and other personnel. Our success depends on our continued ability to attract, retain and motivate highly qualified personnel, such as management, clinical and preclinical personnel, including our executive chairman Richard Stewart and our executive officers John Bencich, Cindy Jacobs, Anthony Clarke and Jaime Xinos. In addition, although we have entered into employment agreements with each of Mr. Stewart, Mr. Bencich, Dr. Jacobs, Dr. Clarke and Ms. Xinos, such agreements permit those executives to terminate their employment with us at any time, subject to providing us with advance written notice.

We may not be able to attract and retain personnel on acceptable terms, if at all, given the competition among numerous pharmaceutical and biotechnology companies for individuals with similar skill sets. In addition, failure to succeed in development and commercialization of cytisinicline may make it more challenging to recruit and retain qualified personnel. The inability to recruit and retain qualified personnel, or the loss of the services of our current personnel may impede the progress of our research, development, and commercialization objectives and would negatively impact our ability to succeed in our product development strategy.

We will need to expand our organization and we may experience difficulties in managing this growth, which could disrupt our operations.

We may need to expand our organization, which may require us to divert a disproportionate amount of our attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in its infrastructure, operational mistakes, loss of business opportunities, loss of employees, and reduced productivity among remaining employees. Expanded growth could require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If we are unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate and/or grow revenue could be reduced and we may not be able to implement our business strategy. Our future financial performance and our ability

to commercialize product candidates and compete effectively will depend, in part, on our ability to effectively manage any future growth.

In the future, we may invest in the development of additional indications for cytisinicline. If we invest in and are unsuccessful in developing additional indications for cytisinicline, our business, financial condition and results of operations may be adversely affected.

In the future, we may invest in the research and development of new indications for cytisinicline to address nicotine addictions associated with the use of e-cigarette, or vaping, products. Given their recent introduction, the use of vaping products is not fully understood which may increase the risk of failure in this area. We are considering potential clinical studies in users of e-cigarettes and have been awarded a grant by the NIH to pursue the initial feasibility of this development. In order to obtain NIH funding to support reimbursement of clinical study costs, the NIH will need to determine that certain milestones under the current award have been achieved. There is no guarantee that we will achieve these milestones or that the NIH agree with our assessment to provide future funding. Even if we successfully achieve these milestones, future grant funding under the award will still be subject to availability of funds at the NIH, and such funding will not be sufficient to cover the full clinical costs of the planned Phase 2 trial. We expect that we will need to invest significant amounts of capital complete the planned Phase 2 trial and pursue development of an e-cigarette cessation indication. If we are unable to provide such additional capital when needed, we may be unable to complete the development, regulatory approval and commercialization of an e-cigarette cessation indication.

The development of additional indications for cytisinicline is highly uncertain. During the research and development cycle, we may expend significant time and resources on developing additional indications without any assurance that we will recoup our investments or that our efforts will be commercially successful. A high rate of failure is inherent in the discovery and development of additional indications, and failure can occur at any point in the process, including late in the process after substantial investment. Further, any new indications may not be accepted by physicians and the medical community at large, and competitors may develop and market equivalent or superior products. Failure to launch commercially successful new indications for cytisinicline after significant investment could have a material adverse effect on our business, financial condition and results of operations.

The outbreak of the novel strain of coronavirus, SARS-CoV-2, which causes COVID-19, could adversely impact our business, including our non-clinical development activities and planned clinical trials.

Public health crises such as pandemics or similar outbreaks could adversely impact our business. As a result of the COVID-19 pandemic, or similar pandemics, we may experience disruptions that could severely impact our business, manufacturing, non-clinical development activities, non-clinical studies and planned clinical trials, including:

- delays or disruptions in non-clinical development activities, including non-clinical experiments and investigational new drug application-enabling good laboratory practice standard toxicology studies due to unforeseen circumstances in supply chain;
- interruption or delays in the operations of the FDA and comparable foreign regulatory agencies, which may impact timelines for regulatory submission, trial initiation and regulatory approval;
- interruption or delays in our CROs and collaborators meeting expected deadlines or complying with regulatory requirements related to non-clinical development activities, non-clinical studies and planned clinical trials;
- interruptions of, or delays in receiving, supplies of our product candidate from Sopharma due to staffing shortages, productions slowdowns or stoppages and disruptions in delivery systems;
- delays or difficulties in any planned clinical site initiation, including difficulties in obtaining IRB approvals, recruiting clinical site investigators and clinical site staff;
- delays or difficulties in enrolling patients in clinical trials;
- increased adverse events or rates of patients withdrawing from any planned clinical trials following enrollment as a result of contracting COVID-19 or being forced to quarantine;
- lower efficacy rates due to diminished patient motivations, increased patient stress, inability to attend behavioral counseling sessions or patients withdrawing from clinical trials as a result of contracting COVID-19 or being forced to quarantine;

- interruption of planned key clinical trial activities, such as clinical trial site data monitoring, due to limitations on travel imposed or recommended by federal or state governments, employers and others or interruption of clinical trial subject visits and study procedures (particularly any procedures that may be deemed non-essential), which may impact the integrity of subject data and planned clinical study endpoints;

- limitations on employee or collaborator resources that would otherwise be focused on the conduct of our non-clinical development activities, non-clinical studies and ongoing or planned clinical trials, including because of sickness of employees or their families, the desire of employees to avoid contact with large groups of people, an increased reliance on working from home or mass transit disruptions; and

- reduced ability to engage with the medical and investor communities due to the cancellation of conferences scheduled throughout the year.

These and other factors arising from the COVID-19 pandemic could worsen as the pandemic continues, which could further adversely impact our ability to conduct non-clinical development activities, non-clinical studies and planned clinical trials and our business generally, and could have a material adverse impact on our operations and financial condition and results. With respect to our ORCA-2 clinical trial, we have experienced delays in enrollment. We may in the future experience more significant delays in enrollment, participant dosing, distribution of clinical trial materials, study monitoring and data analysis that could materially adversely impact our business, timing of trial results, results of operations and overall financial performance in future periods.

In addition, the trading prices for our common stock and other biopharmaceutical companies, as well as the broader equity and debt markets, have been highly volatile as a result of the COVID-19 pandemic and the resulting impact on economic activity. As a result, we may face difficulties raising capital when needed, and any such sales may be on unfavorable terms to us. Further, to the extent we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of existing stockholders will be diluted.

The extent to which the pandemic may impact our business, manufacturing, non-clinical development activities, non-clinical studies and planned clinical trials and will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the ultimate duration of the pandemic, travel restrictions and actions to contain the pandemic or treat its impact, such as social distancing and quarantines or lock-downs in the United States and other countries, business closures or business disruptions and the effectiveness of actions taken in the United States and other countries to contain and treat the disease.

For example, in March 2020, the FDA halted most field inspections of biopharmaceutical facilities and clinical research sites due to travel and contact restrictions imposed by the COVID-19 pandemic. This has restricted the FDA’s ability to perform facilities inspection and has resulted in the delay for the approval of new products. Increasing delay of approvals by the FDA could have a significant negative effect on our business, including the timing of any proposed interactions with the FDA related to any NDA filing and or new product approval.

Our internal computer systems, or those of our third-party collaborators or other service providers, may fail or suffer security breaches and cyber attacks, which could result in a material disruption of our development programs.

We believe that we take reasonable steps that are designed to protect the security, integrity and confidentiality of the information we collect, use, store, and disclose, but inadvertent or unauthorized data access may occur despite our efforts. For example, our system protections may be ineffective or inadequate, or we could be impacted by software bugs or other technical malfunctions, as well as employee error or malfeasance. Additionally, privacy and data protection laws are evolving, and it is possible that these laws may be interpreted and applied in a manner that is inconsistent with our data handling safeguards and practices that could result in fines, lawsuits, and other penalties, and significant changes to our or our third-party collaborators or service providers business practices and products and service offerings. To the extent that the measures we or our third-party collaborators or service providers have taken prove to be insufficient or inadequate, we may become subject to litigation, breach notification obligations, or regulatory or administrative sanctions, which could result in significant fines, penalties, damages, harm to our reputation, or loss of customers. While we have not experienced any material losses as a result of any system failure, accident or security breach to date, we have been the subject of certain phishing attempts in the past. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions. Additionally, a party who circumvents our security measures could, among other effects, appropriate patient information or other proprietary data, cause interruptions in our operations, or expose our collaborators to hacks, viruses, and other disruptions. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. In addition, insurance coverage to compensate for any losses associated with such events may not be adequate to cover all potential losses. The development and maintenance of these systems, controls and processes is costly and requires ongoing monitoring and updating as technologies change and efforts to overcome security measures become increasingly sophisticated.

To the extent that any disruption, security breach, or cyber attack 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, our competitive position could be harmed and the further development and commercialization of our product candidates could be delayed. Depending on the nature of the information compromised, in the event of a data breach or other unauthorized access to our patient data, we may also have obligations to notify patients and regulators about the incident, and we may need to provide some form of remedy, such as a subscription to credit monitoring services, pay significant fines to one or more regulators, or pay compensation in connection with a class-action settlement (including under the new private right of action under the California Consumer Privacy Act of 2018, which is expected to increase security breach litigation). Such breach notification laws continue to evolve and may be inconsistent from one jurisdiction to another. Complying with these obligations could cause us to incur substantial costs and could increase negative publicity surrounding any incident that compromises customer data. Additionally, the financial exposure from the events referenced above could either not be insured against or not be fully covered through any insurance that we may maintain, and there can be no assurance that the limitations of liability in any of our contracts would be enforceable or adequate or would otherwise protect us from liabilities or damages as a result of the events referenced above. Any of the foregoing could have an adverse effect on our business, reputation, financial condition and results of operations.

Risks Related to Our Reliance on Third Parties

We expect to continue to rely on third parties to manufacture cytisinicline for use in clinical trials, and we intend to exclusively rely on Sopharma to produce and process cytisinicline, if approved. Our commercialization of cytisinicline could be stopped, delayed or made less profitable if Sopharma fails to obtain approval of government regulators, fails to provide us with sufficient quantities of product, or fails to do so at acceptable quality levels or prices.

We do not currently have nor do we currently plan to develop the infrastructure or capability internally to manufacture our clinical supplies for use in the conduct of our clinical trials, and we lack the resources and the capability to manufacture cytisinicline on a clinical or commercial scale. We currently exclusively rely on Sopharma to manufacture cytisinicline for use in clinical trials and plan to continue relying on Sopharma to manufacture cytisinicline on a commercial scale, if approved.

Our reliance on Sopharma exposes us to the following additional risks:

- Sopharma might be unable to timely manufacture cytisinicline or produce the quantity and quality required to meet our clinical and commercial needs, if any;
- we may be unable to identify manufacturers other than Sopharma on acceptable terms or at all;
- Sopharma may not be able to execute our manufacturing procedures appropriately;
- Sopharma may not perform as agreed or may not remain in the contract manufacturing business for the time required to supply our clinical trials or to successfully produce, store and distribute our products;
- Sopharma is or will be subject to ongoing periodic unannounced inspection by the FDA and corresponding state agencies to ensure strict compliance with cGMPs and other government regulations and corresponding foreign standards. We do not have control over Sopharma's compliance with these regulations and standards;
- we may not own, or may have to share, the intellectual property rights to any improvements made by Sopharma in the manufacturing process for cytisinicline;
- we do not own all the intellectual property rights to cytisinicline, and Sopharma could license such rights to third parties or begin supplying other third parties with cytisinicline; and
- Sopharma could breach or terminate their agreement with us.

Each of these risks could delay our clinical trials, the approval, if any of cytisinicline by the FDA or the commercialization of cytisinicline or result in higher costs or deprive us of potential product revenue.

We rely on third party contract manufacturing organizations, or CMOs, to package the cytisinicline used in our clinical trials. If any of these CMO's fail to timely deliver supplies needed then our clinical studies could be delayed materially. Third-party manufacturers may fail to perform under their contractual obligations, or may fail to deliver the required commercial product on a timely basis and at commercially reasonable prices. If we are required to identify and qualify an alternate manufacturer, we may be forced to delay or suspend our clinical trials. We expect to continue to depend on third-party contract manufacturers for the foreseeable future.

The manufacture of medical products is complex and requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of medical products often encounter difficulties in production, particularly in scaling up and validating initial production and absence of contamination. These problems include difficulties with production costs and yields, quality control, including stability of the product, quality assurance testing, operator error, shortages of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. Furthermore, if contaminants are discovered in the supply of cytisinicline or in the Sopharma manufacturing facilities, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination. We cannot be assured that any stability or other issues relating to the manufacture of cytisinicline will not occur in the future. Additionally, Sopharma may experience manufacturing difficulties due to resource constraints or as a result of labor disputes or political instability in the countries in which Sopharma conducts its operations. For example, the military conflict between Russia and Ukraine may increase the likelihood of supply interruptions and hinder our ability to find the materials we need to make our product candidate. If Sopharma were to encounter any of these difficulties, or otherwise fail to comply with its contractual obligations, our ability to provide our product candidate to patients in clinical trials could be delayed or suspended. Any delay or interruption in the supply of clinical trial supplies could delay the completion of clinical trials, increase the costs associated with maintaining clinical trial programs and, depending upon the period of delay, require us to commence new clinical trials at additional expense or terminate clinical trials completely. Similar political instability could also harm the commercial production and supply of cytisinicline in the event that cytisinicline is ultimately approved for commercial sale.

In June 2021, Pfizer Inc. halted the distribution of its smoking cessation drug, Chantix (varenicline), after heightened levels, above the FDA's acceptable daily intake limit, of nitrosamines were found in some lots of Chantix pills. In September 2021, Pfizer announced a nationwide recall in the United States of all lots of Chantix and have also withdrawn the product in other countries around the globe. If contaminants, or impurities such as nitrosamines, are discovered in quantities above regulators' thresholds within our supply of cytisinicline, we may need to halt our clinical trials for an extended period of time to investigate and remedy the contamination or impurity, which may potentially delay product development and have a material adverse impact on our business.

We rely on third parties to conduct our clinical trials and perform other services. If these third parties do not successfully perform and comply with regulatory requirements, we may not be able to successfully complete clinical development, obtain regulatory approval or commercialize cytisinicline and our business could be substantially harmed.

We plan to rely upon third-party CROs to conduct, monitor and manage our ongoing clinical programs. We rely on these parties for execution of clinical trials and manage and control only some aspects of their activities. We remain responsible for ensuring that each of our trials is conducted in accordance with the applicable protocol, legal, regulatory, and scientific standards and our reliance on the CROs does not relieve us of our regulatory responsibilities. We and our CROs and other vendors are required to comply with all applicable laws, regulations and guidelines, including those required by the FDA and comparable foreign regulatory authorities for all of our product candidates in clinical development. If we or any of our CROs or vendors fail to comply with applicable laws, regulations and guidelines, the results 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. We cannot be assured that our CROs and other vendors will meet these requirements, or that upon inspection by any regulatory authority, such regulatory authority will determine that efforts, including any of our clinical trials, comply with applicable requirements. Our failure to comply with these laws, regulations and guidelines may require us to repeat clinical trials, which would be costly and delay the regulatory approval process.

If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs in a timely manner or do so on commercially reasonable terms. In addition, our CROs may not prioritize our clinical trials relative to those of other customers and any turnover in personnel or delays in the allocation of CRO employees by the CRO may negatively affect our clinical trials. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, continued development of cytisinicline may be delayed or terminated and we may not be able to meet our current plans with respect to cytisinicline. CROs may also involve higher costs than anticipated, which could negatively affect our financial condition and operations.

We may not be able to establish or maintain the third-party relationships that are necessary to develop or potentially commercialize cytisinicline.

Our business plan relies heavily on third party collaborators, partners, licensees, clinical research organizations, clinical investigators, vendors or other third parties to support our research and development efforts and to conduct clinical trials for cytisinicline. We cannot guarantee that we will be able to successfully negotiate agreements for, or maintain relationships with, these third parties on a commercially reasonable basis, if at all. If we fail to establish or maintain such third-party relationships as anticipated, our business could be adversely affected.

We may be unable to realize the potential benefits of any collaborations which we may enter into with other companies for the development and commercialization of cytisinicline.

We may enter into a collaboration with third parties concerning the development and/or commercialization of cytisinicline; however, there is no guarantee that any such collaboration will be successful. Collaborations may pose a number of risks, including:

- collaborators often have significant discretion in determining the efforts and resources that they will apply to the collaboration, and may not commit sufficient resources to the development, marketing or commercialization of cytisinicline;
- collaborators may not perform their obligations as expected;
- any such collaboration may significantly limit our share of potential future profits from the associated program, and may require us to relinquish potentially valuable rights to cytisinicline, or other potential products or proprietary technologies or grant licenses on terms that are not favorable to us;
- collaborators may cease to devote resources to the development or commercialization of cytisinicline if the collaborators view cytisinicline as competitive with their own products or product candidates;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the course of development, might cause delays or termination of the development or commercialization of cytisinicline, and might result in legal proceedings, which would be time consuming, distracting and expensive;

- collaborators may be impacted by changes in their strategic focus or available funding, or business combinations involving them, which could cause them to divert resources away from the collaboration;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability;
- the collaborations may not result in us achieving revenues to justify such transactions; and
- collaborations may be terminated and, if terminated, may result in a need for us to raise additional capital to pursue further development or commercialization of cytisinicline.

As a result, a collaboration may not result in the successful development or commercialization of cytisinicline.

We enter into various contracts in the normal course of our business in which we indemnify the other party to the contract. In the event we have to perform under these indemnification provisions, it could have a material adverse effect on our business, financial condition and results of operations.

In the normal course of business, we enter into academic, commercial, service, collaboration, licensing, consulting and other agreements that contain indemnification provisions. With respect to our academic and other research agreements, we typically indemnify the institution and related parties from losses arising from claims relating to the products, processes or services made, used, sold or performed pursuant to the agreements for which we have secured licenses, and from claims arising from our or our sublicensees' exercise of rights under the agreement. With respect to our collaboration agreements, we indemnify our collaborators from any third-party product liability claims that could result from the production, use or consumption of the product, as well as for alleged infringements of any patent or other intellectual property right by a third party. With respect to consultants, we indemnify them from claims arising from the good faith performance of their services.

Should our obligation under an indemnification provision exceed applicable insurance coverage or if we were denied insurance coverage, our business, financial condition and results of operations could be adversely affected. Similarly, if we are relying on a collaborator to indemnify us and the collaborator is denied insurance coverage or the indemnification obligation exceeds the applicable insurance coverage, and if the collaborator does not have other assets available to indemnify us, our business, financial condition and results of operations could be adversely affected.

We may rely on third parties to perform many essential services for any of our current or future product candidates that we commercialize, including services related to warehousing and inventory control, distribution, government price reporting, customer service, accounts receivable management, cash collection, and adverse event reporting. If these third parties fail to perform as expected or to comply with legal and regulatory requirements, our ability to commercialize any of our current or future product candidates will be significantly impacted and we may be subject to regulatory sanctions.

We may retain third-party service providers to perform a variety of functions related to the sale and distribution of any of our current or future product candidates, key aspects of which will be out of our direct control. These service providers may provide key services related to warehousing and inventory control, distribution, government price reporting, customer service, accounts receivable management, and cash collection, and, as a result, most of our inventory may be stored at a single warehouse maintained by one such service provider. If we retain a service provider, we would substantially rely on it as well as other third-party providers that perform services for us, including entrusting our inventories of products to their care and handling. If these third-party service providers fail to comply with applicable laws and regulations, fail to meet expected deadlines, or otherwise do not carry out their contractual duties to us, or encounter physical or natural damage at their facilities, our ability to deliver product to meet commercial demand would be significantly impaired and we may be subject to regulatory enforcement action.

In addition, we may engage third parties to perform various other services for us relating to adverse event reporting, safety database management, fulfillment of requests for medical information regarding our product candidates and related services. If the quality or accuracy of the data maintained by these service providers is insufficient, or these third parties otherwise fail to comply with regulatory requirements related to adverse event reporting, we could be subject to regulatory sanctions.

Additionally, if a third-party errs in calculating government pricing information from transactional data in our financial records, it could impact our discount and rebate liability and potentially cause government programs to overpay providers for our products, which could expose us to significant False Claims Act liability and other civil monetary penalties.

Risks Related to Commercialization of Cytisinicline

We face substantial competition and our competitors may discover, develop or commercialize products faster or more successfully than us.

The development and commercialization of new products is highly competitive. We face competition from major pharmaceutical companies, specialty pharmaceutical companies, biotechnology companies, universities and other research institutions worldwide with respect to cytisinicline and the other product candidates that we may seek to develop or commercialize in the future. We are aware that many companies have therapeutics marketed or in development for smoking cessation, including Pfizer Inc., GlaxoSmithKline Plc, Merck & Co., Novartis, Novo Nordisk, Johnson & Johnson, Embera Neurotherapeutics, Inc., 22nd Century Group, Inc., Quit4Good, zpharm, NAL Pharmaceuticals, , Omeros, , Adamed, Aflofarm, Axsome, Amygdala, Antidote Therapeutics, NFL Biosciences, Currax, Palisades Therapeutics, Ro and others.

Many of our competitors have substantially greater financial, name recognition, manufacturing, marketing, research, technical and other resources than us. Additional mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. Further, our competitors may develop new products that are safer, more effective or more cost-efficient than cytisinicline. Large pharmaceutical companies in particular have extensive expertise in non-clinical and clinical testing and in obtaining regulatory approvals for products. In addition, academic institutions, government agencies, and other public and private organizations conducting research may seek patent protection with respect to potentially competitive products or technologies. These organizations may also establish exclusive collaborative or licensing relationships with our competitors. Failure of cytisinicline to effectively compete against established treatment options or in the future with new products currently in development would harm our business, financial condition, results of operations and prospects.

The commercial success of cytisinicline will depend upon the degree of market acceptance by physicians, patients, third-party payors, and others in the medical community. Failure to obtain or maintain adequate reimbursement or insurance coverage for products, if any, could limit our ability to market cytisinicline and decrease our ability to generate revenue.

Even with the approvals from the FDA and comparable foreign regulatory authorities, the commercial success of cytisinicline will depend in part on the healthcare providers, patients, and third-party payors accepting cytisinicline as medically useful, cost-effective, and safe. Cytisinicline may not gain market acceptance by physicians, patients and third-party payors. The degree of market acceptance of cytisinicline will depend on a number of factors, including but not limited to:

- the safety and efficacy, if any, of cytisinicline as demonstrated in clinical trials and potential advantages over competing treatments, if any;
- the clinical indications for which approval is granted, if any, including any limitations or warnings contained in cytisinicline's approved labeling;
- the cost of treatment;
- the perceived ratio of risk and benefit of these therapies by physicians and the willingness of physicians to recommend the product to patients based on such risks and benefits;
- the marketing, sales and distribution support for cytisinicline;
- the publicity concerning cytisinicline or competing products and treatments;
- the pricing and availability of third-party insurance coverage and reimbursement;
- negative perceptions or experiences with our competitor's products may be ascribed to cytisinicline; and
- availability of cytisinicline from other suppliers and/or distributors.

Even if cytisinicline displays a favorable efficacy and safety profile upon approval, market acceptance of cytisinicline remains uncertain. Efforts to educate the medical community and third-party payors on the benefits of cytisinicline, if any, may require significant investment and resources and may never be successful. Additionally, third-party payors, including governmental and private insurers, may also encourage the use of generic products instead of cytisinicline, or a generic version of cytisinicline, which require a prescription or may be available OTC. If our products fail to achieve an adequate level of acceptance by physicians, patients, third-party payors, and other healthcare providers, we will not be able to generate sufficient revenue to become or remain profitable.

The pricing, coverage, and reimbursement of cytisinicline, if any, must be sufficient to support our commercial efforts and other development programs and the availability and adequacy of coverage and reimbursement by third-party payors, including

governmental and private insurers, are essential for most patients to be able to afford treatments. Sales of cytisinicline, if any, will depend substantially, both domestically and abroad, on the extent to which the costs of cytisinicline will be paid for or reimbursed by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or government payors and private payors. If coverage and reimbursement are not available, or are available only in limited amounts, we may have to subsidize or provide cytisinicline for free or we may not be able to successfully commercialize cytisinicline.

In addition, there is significant uncertainty related to the insurance coverage and reimbursement for newly approved products. In the United States, the principal decisions about coverage and reimbursement for new products are typically made by the Centers for Medicare and Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, as CMS decides whether and to what extent a new product will be covered and reimbursed under Medicare. Private payors tend to follow the coverage reimbursement policies established by CMS to a substantial degree. It is difficult to predict what CMS will decide with respect to reimbursement for novel product candidates such as cytisinicline and what reimbursement codes cytisinicline may receive if approved.

Outside the United States, selling operations are generally subject to extensive governmental price controls and other price-restrictive regulations, and we believe the increasing emphasis on cost-containment initiatives in Europe, Canada, and other countries has and will continue to put pressure on the pricing and usage of products. In many countries, the prices of products are subject to varying price control mechanisms as part of national health systems. Price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our products, if any. Accordingly, in markets outside the United States, the potential revenue may be insufficient to generate commercially reasonable revenue and profits.

Moreover, increasing efforts by governmental and private payors in the United States and abroad to limit or reduce healthcare costs may result in restrictions on coverage and the level of reimbursement for new products and, as a result, they may not cover or provide adequate payment for our products. We expect to experience pricing pressures in connection with products due to the increasing trend toward managed healthcare, including the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription products has and is expected to continue to increase in the future. As a result, profitability of cytisinicline, if any, may be more difficult to achieve even if regulatory approval is received.

Sopharma may breach its supply agreement with us and sell cytisinicline into our territories or permit third parties to export cytisinicline into our territories and negatively affect our commercialization efforts of our products in our territories.

We are currently dependent on the exclusivity provisions of our supply agreement with Sopharma to conduct our business and to prevent Sopharma from competing, directly and indirectly, with us in the United States and Western Europe. If Sopharma were to breach the exclusivity provisions of the supply agreement with us and sell or distribute cytisinicline directly into our territories or permit third parties to export cytisinicline into our territories, among other things, the increase in competition within our anticipated markets could have a material adverse effect on our business, results of operations and financial condition.

The illegal distribution and sale by third parties of counterfeit versions of cytisinicline, stolen products, or alternative third-party distribution and sale of cytisinicline could have a negative impact on our financial performance or reputation.

Cytisinicline is not patentable in the United States as it is a naturally occurring substance. As such, third parties are able to manufacture, sell or distribute cytisinicline without royalties or other payments to us and compete with our products in the United States and potentially worldwide and negatively impact our commercialization efforts of our products. We are aware of additional cytisinicline products approved in several European countries and we may not be able to block other third parties from launching generic versions of cytisinicline. Third parties may also sell or distribute cytisinicline as an herbal or homeopathic product. Other than regulatory exclusivity or other limitations, there may be little to nothing to stop these third parties from manufacturing, selling or distributing cytisinicline. Because we have no ability to set rigorous safety standards or control processes over third party manufacturers, sellers or distributors of cytisinicline, excluding Sopharma, these formulations of cytisinicline may be unsafe or cause adverse effects to patients and negatively impact the reputation of cytisinicline as a safe and effective smoking cessation aid.

Third parties could illegally distribute and sell counterfeit versions of cytisinicline, especially on online marketplaces, which do not meet the rigorous manufacturing and testing standards under cGMP. Counterfeit products are frequently unsafe or ineffective, and may even be life-threatening. Counterfeit medicines may contain harmful substances, the wrong dose of the active pharmaceutical ingredient or no active pharmaceutical ingredients at all. However, to distributors and users, counterfeit products may be visually indistinguishable from the authentic version.

Reports of adverse reactions to counterfeit products, increased levels of counterfeiting, or unsafe cytisinicline products could materially affect patient confidence in our cytisinicline product. It is possible that adverse events caused by unsafe counterfeit or other non-Achieve cytisinicline products will mistakenly be attributed to our cytisinicline product. In addition, thefts of inventory at warehouses, plants or while in-transit, which are not properly stored and which are sold through unauthorized channels could adversely impact patient safety, our reputation, and our business. Public loss of confidence in the integrity in cytisinicline as a result of

counterfeiting, theft, or improper manufacturing processes could have a material adverse effect on our business, results of operations, and financial condition.

It is illegal to sell unapproved prescription medicines in the United States. Sopharma's cytisinicline brand is currently approved for sale in certain Central and Eastern European countries. Cytisinicline has not yet received a marketing approval from the FDA and we intend to conduct the requisite clinical trials to obtain approval for the marketing of cytisinicline in the United States and in major global markets. We are aware that products purporting to be Sopharma's cytisinicline brand are available, via third party internet sites, for importation in the United States and other global markets. We have no control over the authenticity of products purchased through these sites, which may be counterfeit or sourced from distributors in Central and Eastern Europe without authorization to sell into the United States or European Union.

We may attempt to form collaborations in the future with respect to cytisinicline, but we may not be able to do so, which may cause us to alter our development and commercialization plans.

We may attempt to form strategic collaborations, create joint ventures or enter into licensing arrangements with third parties with respect to our programs that we believe will complement or augment our existing business. We may face significant competition in seeking appropriate strategic collaborators, and the negotiation process to secure appropriate terms is time consuming and complex. We may not be successful in our efforts to establish such a strategic collaboration for cytisinicline on terms that are acceptable to us, or at all. This may be because cytisinicline may be deemed to be at too early of a stage of development for collaborative effort, our research and development pipeline may be viewed as insufficient, the competitive or intellectual property landscape may be viewed as too intense or risky, or cytisinicline's patent protection insufficient, and/or third parties may not view cytisinicline as having sufficient potential for commercialization, including the likelihood of an adequate safety and efficacy profile.

Any delays in identifying suitable collaborators and entering into agreements to develop and/or commercialize cytisinicline could delay the development or commercialization of cytisinicline, which may reduce our competitiveness even if we reach the market. Absent a strategic collaborator, we would need to undertake development and/or commercialization activities at our own expense. If we elect to fund and undertake development and/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 are unable to do so, we may not be able to develop our product candidate cytisinicline or bring it to market and our business may be materially and adversely affected.

We may not be successful in any efforts to identify, license, discover, develop, or commercialize additional product candidates.

Although a substantial amount of our effort will focus on clinical testing, approval, and potential commercialization of cytisinicline, our sole product candidate, the success of our business is also expected to depend in part upon our ability to identify, license, discover, develop, or commercialize additional product candidates. Research programs to identify new product candidates require substantial technical, financial, and human resources. We may focus our efforts and resources on potential programs or product candidates that ultimately prove to be unsuccessful. Our research programs or licensing efforts may fail to yield additional product candidates for clinical development and commercialization for a number of reasons, including but not limited to the following:

- our research or business development methodology or search criteria and process may be unsuccessful in identifying potential product candidates;
- we may not be able or willing to assemble sufficient resources to acquire or discover additional product candidates;
- our potential product candidates may not succeed in non-clinical or clinical testing;
- our potential product candidates may be shown to have harmful side effects or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval;
- competitors may develop alternatives that render our potential product candidates obsolete or less attractive;
- potential product candidates we develop may be covered by third parties' patents or other exclusive rights;
- the market for a potential product candidate may change during our program so that such a product may become unreasonable to continue to develop;

- a potential product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all; and
- a potential product candidate may not be accepted as safe and effective by patients, the medical community, or third-party payors.

If any of these events occur, we may be forced to abandon our development efforts for a program or programs, or we may not be able to identify, license, discover, develop, or commercialize additional product candidates, which would have a material adverse effect on our business, financial condition or results of operations and could potentially cause us to cease operations.

Risks Related to our Intellectual Property

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

Presently, we have rights to intellectual property through trade secrets, licenses, patents from third parties, and patents and applications that we own. Our product candidate may require specific formulations to work effectively and efficiently and these rights may be held by others. We may be unable to acquire or in-license any compositions, methods of use, processes or other third-party intellectual property rights from third parties that we identify. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment. If we are unable to successfully obtain rights to third-party intellectual property rights, our business, financial condition and prospects for growth could suffer.

If we are unable to maintain effective proprietary rights for our product candidate or any future product candidates, we may not be able to compete effectively in our proposed markets.

We currently rely primarily on trade secret protection and on confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. Trade secrets can be difficult to protect, however, and even where they are protected they generally provide less intellectual property protection to the holder of the trade secret than to a holder of a patent. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors, and contractors. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors.

Although we expect all of our employees and consultants to assign their inventions to us, and all of our employees, consultants, advisors, and any third parties who have access to our proprietary know-how, information, or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Misappropriation or unauthorized disclosure of our trade secrets could impair our competitive position and may have a material adverse effect on our business, financial condition or results of operations. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating the trade secret.

Third-party claims of intellectual property infringement may prevent or delay our development and commercialization efforts.

We are currently developing cytisinicline for smoking cessation. Our commercial success depends in part on our ability to develop, manufacture, market and sell our product candidates and use our proprietary technology without infringing the patent rights of third parties. We are not aware of any patents or patent applications that would prevent the development, manufacture or marketing of cytisinicline for smoking cessation.

We are aware of U.S. and foreign patents and pending patent applications owned by third parties that cover certain other therapeutic uses of cytisinicline. We are currently monitoring these patents and patent applications. We may in the future pursue available

proceedings in the U.S. and foreign patent offices to challenge the validity of these patents and patent applications. In addition, or alternatively, we may consider whether to seek to negotiate a license of rights to technology covered by one or more of such patents and patent applications for these certain additional therapeutic uses. If any third-party patents or patent applications cover our product candidates or technologies in other therapeutic uses, we may not be free to manufacture or market our product candidates for additional therapeutic uses, absent such a license, which may not be available to us on commercially reasonable terms, or at all.

It is also possible that we have failed to identify relevant third-party patents or applications. For example, applications filed before November 29, 2000 and applications filed after that date that will not be filed outside the United States remain confidential until patents issue. Moreover, it is difficult for industry participants, including us, to identify all third-party patent rights that may be relevant to our product candidates and technologies because patent searching is imperfect due to differences in terminology among patents, incomplete databases and the difficulty in assessing the meaning of patent claims. We may fail to identify relevant patents or patent applications or may identify pending patent applications of potential interest but incorrectly predict the likelihood that such patent applications may issue with claims of relevance to our technology. In addition, we may be unaware of one or more issued patents that would be infringed by the manufacture, sale or use of a current or future product candidate, or we may incorrectly conclude that a third-party patent is invalid, unenforceable or not infringed by our activities. Additionally, pending patent applications that have been published can, subject to specified limitations, be later amended in a manner that could cover our technologies, our product candidates or the use of our product candidates.

There have been many lawsuits and other proceedings involving patent and other intellectual property rights in the pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions, and reexamination proceedings before the USPTO and corresponding foreign patent offices. U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are developing our product candidate. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidate may be subject to claims of infringement of the patent rights of third parties.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our product candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure.

We intend to rely on patent rights for certain aspects of our product candidates and certain future product candidates. If we are unable to obtain or maintain an adequate proprietary position from this approach, we may not be able to compete effectively in our markets.

Although we rely or will rely primarily on trade secret protection as part of our intellectual property rights strategies, we also intend to rely on patent rights to protect certain aspects of our technologies and upon the patent rights of third parties from which we license certain of our technologies.

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

The patent position of pharmaceutical companies generally is highly uncertain and involves complex legal and factual questions for which legal principles remain unsolved. The patent applications that we own may fail to result in issued patents with claims that cover our product candidates in the United States or in other foreign countries. There is no assurance that all potentially relevant prior art relating to our patent applications or our patents (once issued) have been found, which can invalidate a patent or prevent a patent from issuing from a pending patent application. Even if patents do successfully issue, and even if such patents cover our future product candidates, third parties may challenge their validity, enforceability, or scope, which may result in such patents being narrowed, found unenforceable or invalidated. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property, provide exclusivity for our future product candidates, or prevent others from designing around our claims. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

We cannot offer any assurances about which, if any, patents will issue, the breadth of any such patent or whether any issued patents will be found invalid and unenforceable or will be threatened by third parties. Any successful opposition to these patents or any other

patents owned by or licensed to us after patent issuance could deprive us of rights necessary for the successful commercialization of any future product candidates that we may develop. Further, if we encounter delays in regulatory approvals, the period of time during which we could market a future product candidate under patent protection could be reduced.

If we cannot obtain and maintain effective protection of exclusivity from our regulatory efforts and intellectual property rights, including patent protection or data exclusivity, for our product candidates, we may not be able to compete effectively and our business and results of operations would be harmed.

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

Obtaining and enforcing patents in the biopharmaceutical industry involves both technological and legal complexity, and is therefore costly, time-consuming, and inherently uncertain. In addition, the United States has recently enacted and is currently implementing wide-ranging patent reform legislation. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. 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, if any. Depending on decisions by the U.S. Congress, the federal courts and the U.S. Patent and Trademark Office, or the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

In *Assoc. for Molecular Pathology v. Myriad Genetics, Inc*., the U.S. Supreme Court held that certain claims to naturally occurring substances are not patentable. Cytisinicline is a naturally occurring product and is not patentable. Our intellectual property strategy involves novel formulations of cytisinicline and there is no guarantee that such patents will be issued or if issued, will be broad enough to prevent competitors from developing competing cytisinicline products. Although we do not believe that any patents that may issue from our pending patent applications directed at our product candidate, if issued in their currently pending forms, as well as patent rights licensed by us, will be found invalid based on this decision, we cannot predict how future decisions by the courts, the U.S. Congress or the USPTO may impact the value of our patent rights. There could be similar changes in the laws of foreign jurisdictions that may impact the value of our patent rights or our other intellectual property rights.

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

We employ individuals who were previously employed at other biotechnology or pharmaceutical companies. Although we have written agreements and make every effort to ensure that our employees, consultants, and independent contractors do not use the proprietary information or intellectual property rights of others in their work for us, we may in the future be subject to any claims that our employees, consultants, or independent contractors have wrongfully used or disclosed confidential information of third parties. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could adversely impact our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

It is difficult and costly to protect our proprietary rights and as a result we may not be able to ensure their protection. In addition, patents have a limited lifespan and will eventually expire.

Market exclusivity awarded by the FDA upon the approval of an NDA is limited in scope and duration. Our commercial success will depend in part on obtaining, maintaining, enforcing, and defending against third-party challenges, patent and trade secret protection for our current and future product candidates that we may develop, license or acquire, as well as the related manufacturing methods. We will be able to protect our technologies from unauthorized use by third parties to the extent that the technologies are covered by valid and enforceable patents or trade secrets.

The patent prosecution process is expensive and time consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Moreover, should we enter into additional collaborations we may be required to consult with or cede control to collaborators regarding the prosecution, maintenance, and enforcement of our patent applications and patents. Therefore, these patents and patent applications may not be prosecuted and enforced in a manner consistent with the best interests of our business. The patent positions of pharmaceutical and biotechnology companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in pharmaceutical or biotechnology patents has emerged to

date in the United States. The patent situation outside the United States is even more uncertain. Changes in either the patent laws or in interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in our patents and patent applications or in third-party patents and patent applications. The degree of future protection for our proprietary rights is uncertain because legal means afford only limited protection and may not adequately protect our rights or permit us to gain or keep our competitive advantage. Moreover, the patent application process is also subject to numerous risks and uncertainties, and there can be no assurance that we or any of our future development partners will be successful in protecting any of our current or future product candidates that we may develop, license, or acquire by obtaining and defending patents. For example:

- we may not have been the first to conceive of and reduce to practice the inventions covered by each of our pending patent applications and issued patents;
- we may not have been the first to file patent applications for these inventions;
- others may independently develop similar or alternative technologies or duplicate any of our product candidates or technologies;
- it is possible that none of the pending patent applications will result in issued patents;
- the issued patents may not cover commercially viable active products, may not provide us with any competitive advantages, or may be successfully challenged by third parties;
- we may not develop additional proprietary technologies that are patentable;
- patents of others may have an adverse effect on our business;
- noncompliance with requirements of governmental patent agencies can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction, potentially allowing competitors to enter the market earlier than would otherwise have been the case;
- our competitors, many of whom have substantially greater resources than we do and many of whom have made significant investments in competing technologies, may seek or may have already obtained patents that will limit, interfere with, or eliminate our ability to make, use, and sell our potential product candidates; or
- there may be significant pressure on the U.S. government and international governmental bodies to limit the scope of available patent protection both inside and outside the United States for disease treatments that prove successful, as a matter of public policy regarding worldwide health concerns.

Patents have a limited lifespan. In most countries, including the United States, the expiration of a patent is typically 20 years from the date that the application for the patent is filed. Various extensions of patent term may be available in particular countries; however, in all circumstances the life of a patent, and the protection it affords, has a limited term. If we encounter delays in obtaining regulatory approvals, the period of time during which we could market a product under patent protection could be reduced. We expect to seek extensions of patent terms where these are available in any countries where we are prosecuting patents. Such possible extensions include those permitted under the Drug Price Competition and Patent Term Restoration Act of 1984 in the United States, which permits a patent term extension of up to five years to cover an FDA-approved product. The actual length of the extension will depend on the amount of patent term lost while the product was in clinical trials. However, the applicable authorities, including the U.S. Patent and Trademark Office, or USPTO, and the FDA in the United States, and any equivalent regulatory authority in other countries, may not agree with our assessment of whether such extensions are available, and may refuse to grant extensions to our patents, or may grant more limited extensions than we request. If this occurs, our competitors may be able to take advantage of our investment in development and clinical trials by referencing our clinical and preclinical data, and then may be able to launch their product earlier than might otherwise be the case.

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

The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment, and other similar provisions during the patent prosecution process. Periodic maintenance fees, renewal fees, annuity fees, and various other governmental fees on patents or patent applications will be due to be paid to the USPTO and various patent agencies

outside of the United States in several stages over the lifetime of the patents and applications. We have systems in place to remind us to pay these fees, and we employ and rely on reputable law firms and other professionals to effect payment of these fees to the USPTO and non-U.S. patent agencies for the patents and patent applications we own and those that we in-license. We also employ reputable law firms and other professionals to help us comply with the various documentary and other procedural requirements with respect to the patents and patent applications that we own and those that we in-license. In some cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, our competitors might be able to enter the market and this circumstance would have a material adverse effect on our business.

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

Competitors may infringe our issued patents, our in-licensed patents, or other intellectual property that we own or in-license. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents. In addition, in a patent infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, in whole or in part; construe the patent's claims narrowly; or refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly. 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.

Most of our competitors are larger than we are and have substantially greater resources than we do. They are, therefore, likely to be able to sustain the costs of complex patent litigation longer than we could. In addition, the uncertainties associated with litigation could have a material adverse effect on our ability to raise the funds necessary to continue our clinical trials, continue our internal research programs, in-license needed technology, or enter into development partnerships that would help us bring our product candidates to market.

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

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

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

Risks Related to Our Common Stock

The price for our common stock is volatile.

The market prices for our common stock and thatof early-stage pharmaceutical, biotechnology and other life sciences companies have historically been particularly volatile. Some of the factors that may cause the market price of our common stock to fluctuate include:

- our ability to raise additional capital, the terms of such capital, and our ability to continue as a going concern;

- the ability of us or our partners to develop cytisinicline and other product candidates and conduct clinical trials that demonstrate such product candidates are safe and effective;
- the ability of us or our partners to obtain regulatory approvals for cytisinicline or other product candidates, and delays or failures to obtain such approvals;
- failure of any of our product candidates to demonstrate safety and efficacy, receive regulatory approval and achieve commercial success;
- failure to maintain our existing third-party license, manufacturing and supply agreements;
- failure by us or our licensors to prosecute, maintain, or enforce our intellectual property rights;
- changes in laws or regulations applicable to our candidates;
- any inability to obtain adequate supply of product candidates or the inability to do so at acceptable prices;
- adverse regulatory authority decisions;
- introduction of new or competing products by our competitors;
- failure to meet or exceed financial and development projections we may provide to the public;
- the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- announcements of significant acquisitions, strategic partnerships, joint ventures, or capital commitments by us or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters, and our ability to obtain intellectual property protection for our technologies;
- additions or departures of key personnel;
- significant lawsuits, including intellectual property or stockholder litigation;
- if securities or industry analysts do not publish research or reports about us, or if they issue an adverse or misleading opinion regarding our business and stock;
- changes in the market valuations of similar companies;
- general market or macroeconomic conditions and geopolitical conditions, including the current global economic recession caused by the COVID-19 pandemic and the increasingly volatile global economic conditions resulting from the conflict in Ukraine;
- sales of our common stock us or our stockholders in the future;
- trading volume of our common stock;
- adverse publicity relating to our markets generally, including with respect to other products and potential products in such markets;
- changes in the structure of healthcare payment systems;
- period-to-period fluctuations in our financial results; and
- tweets or other social media posts related to our market and industry.

Moreover, the stock markets in general have experienced substantial volatility that has often been unrelated to the operating performance of individual companies. These broad market fluctuations may also adversely affect the trading price of our common stock. An increase in the market price of our common stock, which is uncertain and unpredictable, may be the sole source of gain from an investment in our common stock. An investment in our common stock may not be appropriate for investors who require dividend income. We have never declared or paid cash dividends on our capital stock and do not anticipate paying any cash dividends on our capital stock in the foreseeable future. We currently intend to retain all available funds and any future earnings to fund the development and growth of our business. As a result, capital appreciation, if any, of our common stock will be the sole source of gain for stockholders for the foreseeable future. Accordingly, an investment in our common stock may not be appropriate for investors who require dividend income or investors who are not prepared to bear a significant risk of losses from such an investment.

The sale of additional shares of common stock pursuant to our existing equity sale agreements or the conversion of our convertible debt into shares of common stock, may cause the price of our common stock to decline and result in dilution to our existing stockholders.

In September 2017 we entered into a purchase agreement, or the Purchase Agreement, with Lincoln Park Capital Fund, LLC, or LPC, which was amended in March 2020, pursuant to which we have the right, from time to time, in our sole discretion and subject to certain conditions, to direct LPC to purchase additional shares of common stock having an aggregate value of approximately $10.0 million and we have exercised this right. We have directed LPC to purchase additional shares and may further direct LPC to purchase additional shares as often as every business day over the 54-month term of the Purchase Agreement in increments of up to 7,500 shares of common stock. The purchase price of shares of common stock pursuant to the Purchase Agreement have been and will be based on prevailing market prices of common stock at the time of sale without any fixed discount, and we have controlled and will control the timing and amount of any sales of common stock to LPC. In addition, we have directed and we may direct LPC in the future to purchase additional amounts as accelerated purchases.

In December 2021, we entered into an At-the-Market Offering Sales Agreement, or ATM, with Virtu Americas, LLC, as sales agent, pursuant to which we may sell shares of common stock with an aggregate offering price of up to $25 million. Also in December 2021, we entered into a $25.0 million contingent convertible debt agreement, or Debt Agreement, with Silicon Valley Bank, or SVB, and SVB Innovation Credit Fund VIII, L.P., or, together with SVB, the Lenders. As part of the contingent convertible debt agreement, the Lenders funded $15.0 million in the form of convertible indebtedness, or Convertible Debt, at closing. Subject to certain terms and conditions, the Lenders may convert all or any part of the outstanding Convertible Debt and accrued and unpaid interest at any time prior to maturity into shares of our common stock at a conversion price equal to $9.34 per share, subject to customary anti-dilution adjustments. Additionally, all outstanding Convertible Debt, including accrued and unpaid interest, will mandatorily convert into shares of our common stock, at the conversion price, on such date, if any, when the closing price per share of our common stock has been equal to or greater than $24.00 for 30 consecutive trading days prior to such date.

The sale of additional shares of our common stock pursuant to the Purchase Agreement with LPC or our ATM, or the conversion of the Convertible Debt into shares of our common stock, would have a dilutive impact on our existing stockholders. Sales by us to LPC, or under the ATM, or the conversion of the Convertible Debt, could cause the market price of our common stock to decline significantly. Sales of our common stock under the Purchase Agreement, or the ATM, the conversion of the Convertible Debt or the perception that such events will occur, could also encourage short sales by third parties, which could contribute to the further decline of the price of our common stock. Additionally, the sale of a substantial number of shares of our common stock under the Purchase Agreement or ATM, the conversion of the Convertible Debt or the perception that such events will occur, could make it more difficult for us to sell equity or equity-related securities in the future at a time and at a price that we might otherwise wish.

Because our merger resulted in an ownership change under Section 382 of the U.S. Internal Revenue Code for OncoGenex, pre-merger net operating loss carryforwards and certain other tax attributes are now subject to limitations.

If a corporation undergoes an "ownership change" within the meaning of Section 382 of the U.S. Internal Revenue Code, the corporation's net operating loss carryforwards and certain other tax attributes arising from before the ownership change are subject to limitations on use after the ownership change. In general, an ownership change occurs if there is a cumulative change in the corporation's equity ownership by certain stockholders that exceeds fifty percentage points over a rolling three-year period. Similar rules may apply under state tax laws. Our 2017 merger involving OncoGenex and Achieve Life Sciences, Inc. resulted in an ownership change for OncoGenex and, accordingly, OncoGenex's net operating loss carryforwards and certain other tax attributes will be subject to limitations on their use after the merger. Additional ownership changes in the future could result in additional limitations on the combined organization's net operating loss carryforwards. Consequently, even if we achieve profitability, we may not be able to utilize a material portion of our net operating loss carryforwards and other tax attributes, which could have a material adverse effect on cash flow and results of operations.

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

The trading market for our common stock is influenced by the research and reports that equity research analysts publish about us and our business. We do not have any control over the equity research analysts that provide research coverage of our common stock or the content and opinions included in their reports. The price of our stock could decline if one or more equity research analysts downgrades our stock or issue other unfavorable commentary or research. If one or more equity research analysts ceases coverage of our company or fails to publish reports on us regularly, demand for our stock could decrease, which in turn could cause our stock price or trading volume to decline.

General Risk Factors

We are at risk of securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities, including in circumstances where such declines occur in close proximity to the announcement of clinical trial results. Additionally, our stock price and those of other biotechnology and biopharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

We incur costs and demands upon management as a result of complying with the laws and regulations affecting public companies.

We incur significant legal, accounting and other expenses associated with public company reporting requirements. We also incur costs associated with corporate governance requirements, including requirements under the Sarbanes-Oxley Act, as well as rules implemented by the SEC and The Nasdaq Capital Market. These rules and regulations impose significant legal and financial compliance costs and make some activities more time-consuming and costly. In addition, it may be difficult for us to attract and retain qualified individuals to serve on our board of directors or as executive officers, which may adversely affect investor confidence and could cause our business or stock price to suffer.

If we raise additional capital, the terms of the financing transactions may cause dilution to existing stockholders or contain terms that are not favorable to us.

In the future, we plan to raise additional capital through private placements or public offerings of our equity or debt securities. We cannot be certain that additional funding will be available on acceptable terms, if at all. To the extent that we raise additional financing by issuing equity securities, we may do so at a price per share that represents a discount to the then-current per share trading price of our common stock and our stockholders may experience significant dilution. Any debt financing, if available, may involve restrictive covenants, such as limitations on our ability to incur additional indebtedness, limitations on our ability to acquire or license intellectual property rights and other operating restrictions that could adversely affect our ability to conduct our business.

Anti-takeover provisions under Delaware law could make an acquisition of us more difficult and may prevent attempts by our stockholders to replace or remove our management.

Because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporate Law, which prohibits stockholders owning in excess of 15% of our outstanding voting stock from merging or combining with us. Although we believe these provisions collectively will provide for an opportunity to receive higher bids by requiring potential acquirors to negotiate with our board of directors, they would apply even if the offer may be considered beneficial by some stockholders. In addition, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove then current management by making it more difficult for stockholders to replace members of the board of directors, which is responsible for appointing the members of management.

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

Our bylaws provide that the Court of Chancery of the State of Delaware is the sole and exclusive forum for any derivative action or proceeding brought on our behalf, any action asserting a breach of fiduciary duty owed by any of our directors, officers or other employees to us or our stockholders, any action asserting a claim against us arising pursuant to any provisions of the Delaware General Corporation Law, our certificate of incorporation or our bylaws, or any action asserting a claim against us that is governed by the internal affairs doctrine. The choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and

our directors, officers and other employees. If a court were to find the choice of forum provision contained in the bylaws to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions.

We are a smaller reporting company and we cannot be certain if the reduced disclosure requirements applicable to smaller reporting companies will make our common stock less attractive to investors.

We are currently a "smaller reporting company" as defined in the Securities Exchange Act of 1934, and are thus allowed to provide simplified executive compensation disclosures in our filings, are exempt from the provisions of Section 404(b) of the Sarbanes-Oxley Act requiring that an independent registered public accounting firm provide an attestation report on the effectiveness of internal control over financial reporting and have certain other decreased disclosure obligations in our SEC filings. We cannot predict whether investors will find our common stock less attractive because of our reliance on any of 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 stock price may be more volatile.

U.S. federal tax reform and changes in other tax laws could increase our tax burden and adversely affect our business and financial condition.

In December 2017, the U.S. government enacted comprehensive tax legislation, the Tax Cuts and Jobs Act of 2017, significantly reforming the Internal Revenue Code of 1986, as amended. These changes include, among others, (i) a permanent reduction to the corporate income tax rate, (ii) a partial limitation on the deductibility of business interest expense, (iii) a shift of the U.S. taxation of multinational corporations from a tax on worldwide income to a territorial system (along with certain rules designed to prevent erosion of the U.S. income tax base) and (iv) a one-time tax on accumulated offshore earnings held in cash and illiquid assets, with the latter taxed at a lower rate.

In addition, beginning in 2022, the recently enacted tax legislation will require research and experimental expenditures to be capitalized and amortized ratably over a five-year period. Any such expenditures attributable to research conducted outside the United States must be capitalized and amortized over a 15-year period.

Notwithstanding the reduction in the corporate income tax rate, the overall impact of this tax reform is uncertain, and our business and financial condition could be adversely affected. Furthermore, it is uncertain if and to what extent various states will conform to the enacted federal tax law or any newly enacted federal legislation. In addition, new legislation or regulation which could affect our tax burden could be enacted by any governmental authority. We cannot predict the timing or extent of such tax-related developments which could have a negative impact on our financial results. Additionally, we use our best judgment in attempting to quantify and reserve for these tax obligations. However, a challenge by a taxing authority, our ability to utilize tax benefits such as carryforwards or tax credits, or a deviation from other tax-related assumptions could have a material adverse effect on our business, results of operations, or financial condition.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

We have a business office located in Vancouver, British Columbia.

On November 19, 2018, we entered into a lease agreement for our office space in Vancouver, British Columbia, which commenced on February 1, 2019, and has a four-year term. Pursuant to this lease, we rent approximately 2,367 square feet of office space. The annual rent is approximately $0.1 million.

We believe that the facility we currently lease is sufficient for our anticipated near-term needs.

ITEM 3. LEGAL PROCEEDINGS

From time to time, we may be involved in litigation relating to claims arising out of our operations in the normal course of business. We are not currently a party to any legal proceedings, the adverse outcome of which, in management's opinion, individually or in the aggregate, would have a material adverse effect on the results of our operations or financial position. There are no material proceedings to which any director, officer or any of our affiliates, any owner of record or beneficially of more than five percent of any class of our voting securities, or any associate of any such director, officer, our affiliates, or security holder, is a party adverse to us or our consolidated subsidiary or has a material interest adverse thereto.

ITEM 4. MINE SAFETY DISCLOSURE

Not applicable.

PART II

ITEM 5. MARKET FOR THE REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Our common stock first began trading on the Nasdaq National Market under the symbol "SNUS" on October 12, 1995. In connection with a corporate transaction and name change, our common stock commenced trading on the Nasdaq Capital Market under the stock symbol "OGXI", effective August 21, 2008. Following the completion of a corporate transaction and name change, our common stock commenced trading on the Nasdaq Capital Market under the stock symbol "ACHV", effective August 2, 2017.

No cash dividends have been paid on our common stock, and we do not anticipate paying any cash dividends in the foreseeable future. As of February 22, 2022, there were approximately 16 stockholders of record. A substantially greater number of holders of our common stock are "street name" or beneficial holders, whose shares of record are held by banks, brokers, and other financial institutions.

The information required by this item regarding equity compensation plan information is set forth in Part III, Item 12 of this Annual Report on Form 10-K.

No purchases of equity securities during the year ended December 31, 2021 were made by us or on our behalf.

On February 4, 2022, we issued 3,584 in unregistered shares of common stock pursuant to Section 4(a)(2) of the Securities Act to one of our vendors as part of a non-monetary barter transaction for the settlement of trade payables owed.

ITEM 6. RESERVED

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

Forward-Looking Statements

This Annual Report on Form 10-K contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements involve a number of risks and uncertainties. We caution readers that any forward-looking statement is not a guarantee of future performance and that actual results could differ materially from those contained in the forward-looking statement. These statements are based on current expectations of future events. Such statements include, but are not limited to, statements about future financial and operating results, plans, objectives, expectations and intentions, costs and expenses, interest rates, outcome of contingencies, financial condition, results of operations, liquidity, business strategies, cost savings, objectives of management, the impact of the COVID-19 pandemic on our business and other statements that are not historical facts. You can find many of these statements by looking for words like "believes," "expects," "anticipates," "estimates," "may," "should," "will," "could," "plan," "intend," or similar expressions in this Annual Report on Form 10-K or in documents incorporated by reference into this Annual Report on Form 10-K. We intend that such forward-looking statements be subject to the safe harbors created thereby. Examples of these forward-looking statements include, but are not limited to:

- progress and preliminary and future results of any clinical trials;
- anticipated regulatory filings, requirements and future clinical trials;
- the effects of the COVID-19 pandemic on our business and financial results;
- the performance of, and our ability to obtain sufficient supply of cytisinicline in a timely manner from, third-party suppliers and manufacturers;
- timing and plans for the expansion of our focus to address other methods of nicotine addiction;
- timing and amount of future contractual payments, product revenue and operating expenses; and
- market acceptance of our products and the estimated potential size of these markets.

These forward-looking statements are based on the current beliefs and expectations of our management and are subject to significant risks and uncertainties. If underlying assumptions prove inaccurate or unknown risks or uncertainties materialize, actual results may differ materially from current expectations and projections. Factors that might cause such a difference include those discussed in Item 1A "Risk Factors," as well as those discussed elsewhere in the Annual Report on Form 10-K.

You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of this Annual Report on Form 10-K or, in the case of documents referred to or incorporated by reference, the date of those documents.

All subsequent written or oral forward-looking statements attributable to us or any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to in this section. We do not undertake any obligation to release publicly any revisions to these forward-looking statements to reflect events or circumstances after the date of this Annual Report on Form 10-K or to reflect the occurrence of unanticipated events, except as may be required under applicable U.S. securities law. If we do update one or more forward-looking statements, no inference should be drawn that we will make additional updates with respect to those or other forward-looking statements.

Overview

We are a clinical-stage pharmaceutical company committed to the global development and commercialization of cytisinicline for smoking cessation and nicotine addiction. With more than one billion smokers globally and over 34 million smokers in the United States alone, smoking remains the leading cause of preventable disease and death, responsible for more than eight million deaths annually worldwide. Our primary focus is to address this global epidemic.

We also plan to expand our focus to address other methods of nicotine addiction such as e-cigarettes/vaping The use of e-cigarettes continues to be widespread, with most recent reports from the Centers for Disease Control and Prevention indicating nearly 11 million adult users in the United States alone in 2019. While e-cigarettes have been historically viewed as less harmful than combustible cigarettes, their long-term safety remains controversial. In a recent study that we conducted surveying approximately 500 users of nicotine vaping devices or e-cigarettes, approximately 73% of participants responded that they intend to quit vaping within the next three to 12 months. Of those who intended to quit even sooner, within the next 3 months, more than half stated they would be extremely likely to try a new prescription product to help them do so. We believe that cytisinicline, if approved, could be the first prescription drug indicated for vape and e-cigarette users who are ready to quit their nicotine addiction.

Our management team has significant experience in growing emerging companies focused on the development of under-utilized pharmaceutical compounds to meet unmet medical needs. We intend to use this experience to develop and ultimately commercialize cytisinicline either directly or via strategic collaborations.

Cytisinicline is an established smoking cessation treatment that has been approved and marketed in Central and Eastern Europe by Sopharma AD for over 20 years. Sopharma's marketed product is a 1.5 mg cytisinicline dosage administered on a declining titration schedule over a 25 day period. We are evaluating an improved dosing and administration of cytisinicline that is expected to improve compliance and outcomes for smokers. We have an exclusive license and supply agreement with Sopharma for the development and commercialization of cytisinicline outside of Sopharma's territories which are predominately located in Central and Eastern Europe. It is estimated that over 20 million people have used Sopharma's cytisinicline product to help treat nicotine addiction, including over 2,700 smokers in investigator-conducted, Phase 3 clinical trials in Europe and New Zealand.

Cytisinicline is a naturally occurring, plant-based alkaloid. Cytisinicline is structurally similar to nicotine and has a well-defined, dual-acting mechanism of action that is both agonistic and antagonistic. It is believed to aid in smoking cessation and the treatment of nicotine addiction by interacting with nicotine receptors in the brain by reducing the severity of nicotine withdrawal symptoms through agonistic effects on nicotine receptors and by reducing the reward and satisfaction associated with nicotine through antagonistic properties.

In 2018, the U.S. Adopted Names Council adopted cytisinicline as the non-proprietary, or generic, name for the substance also known as cytisine.

We have no products approved for commercial sale and have not generated any revenue from product sales to date. We have never been profitable and have incurred operating losses in each year since inception. Our net loss was $33.2 million for the year ended December 31, 2021. As of December 31, 2021, we had an accumulated deficit of $93.6 million, cash and cash equivalents balance of $43.0 million and a positive working capital balance of $40.0 million. During the year ended December 31, 2021, net cash used in operations was $29.4 million.

Cytisinicline Ongoing and Recent Clinical Developments

Clinical Trials

Ongoing Company-Sponsored Phase 3 Clinical Trials

In October 2020, we initiated the Phase 3 ORCA-2 clinical trial. ORCA-2 is evaluating the efficacy and safety of 3 mg cytisinicline dosed three times daily compared to placebo in adult smokers at 17 clinical sites in the United States. ORCA-2 participants have been randomized to one of three study arms to determine the smoking cessation efficacy and safety profile of cytisinicline when administered for either 6 or 12 weeks, compared to placebo. All subjects receive standard behavioral support and have been assigned to one of the following groups:

- Arm A: 12 weeks of placebo
- Arm B: 6 weeks of cytisinicline, followed by 6 weeks of placebo
- Arm C: 12 weeks of cytisinicline

The primary outcome measure of success in the ORCA-2 trial is biochemically verified continuous abstinence during the last 4 weeks of treatment in the 6 and 12-week cytisinicline treatment arms compared to placebo. Each treatment arm will be compared independently to the placebo arm, and the trial will be determined to be successful if either or both of the cytisinicline treatment arms show a statistical benefit compared to placebo. Secondary outcome measures will be conducted to assess continued abstinence rates through 6 months from the start of study treatment. In January 2022, we announced that the last study follow-up visit for the last subject enrolled in the trial was completed in December 2021. A total of 810 adult smokers were randomized. Topline ORCA-2 data results are expected to be reported during the second quarter of 2022.

In January 2022, we initiated our Phase 3 ORCA-3 clinical trial. ORCA-3 is a confirmatory Phase 3 trial required for registrational approval of cytisinicline in the United States. The Phase 3 trial will evaluate the efficacy and safety of 3 mg cytisinicline dosed 3 times daily compared to placebo in 750 adult smokers at 15 clinical sites. ORCA-3 participants will be randomized to one of three study arms to evaluate cytisinicline administered for either 6 or 12 weeks, compared to placebo. All subjects will receive standard behavioral support and will be assigned to one of the following groups:

- Arm A: 12 weeks of placebo

- Arm B: 6 weeks of cytisinicline, followed by 6 weeks of placebo
- Arm C: 12 weeks of cytisinicline

The primary outcome measure of success in the ORCA-3 trial is biochemically verified continuous abstinence during the last four weeks of treatment in the 6 and 12-week cytisinicline treatment arms compared with placebo. Each treatment arm will be compared independently to the placebo arm, and the trial will be determined to be successful if either or both of the cytisinicline treatment arms show a statistical benefit compared to placebo. Secondary outcome measures will be conducted to assess continued abstinence rates through 6 months from the start of study treatment.

Completed Company-Sponsored Phase 2 Clinical Trial

In June 2019, we announced positive top line results for the Phase 2b ORCA-1 trial and defined the dose selection of 3 mg, three times daily, or TID, for our Phase 3 development. ORCA-1 was the first trial in our Ongoing Research of Cytisinicline for Addiction Program, or ORCA Program, that aims to evaluate the effectiveness of cytisinicline for smoking cessation, nicotine addiction therapy, and potential benefit in other indications.

ORCA-1 was initiated in October 2018 and evaluated 254 smokers in the United States. The trial evaluated both 1.5 mg and 3 mg doses of cytisinicline on the standard declining titration schedule as well as a more simplified TID dosing schedule, both over 25 days. The trial was randomized and blinded to compare the effectiveness of the cytisinicline doses and schedules to respective placebo groups. Subjects were treated for 25 days, provided behavioral support, and followed up for an additional four weeks to assess continued smoking abstinence after the 25-day treatment.

The primary endpoint in the study was the reduction in daily smoking, a self-reported measure. Three of the four cytisinicline treatment arms demonstrated a statistically significant reduction, $p<0.05$, compared to placebo. The fourth arm trended to significance ($p= 0.052$). Across all treatment arms, over the 25-day treatment period, subjects on cytisinicline experienced a 74-80% median reduction in the number of cigarettes smoked, compared to a 62% reduction in the placebo arms.

The secondary endpoint of the trial was a 4-week continuous abstinence rate, which is the relevant endpoint for regulatory approval. All cytisinicline treatment arms showed significant improvements in abstinence rates compared to the placebo arms. The most impressive results were observed in the 3 mg TID cytisinicline arm which demonstrated a 50% abstinence rate at week 4, compared to 10% for placebo ($p<0.0001$) and a continuous abstinence rate, weeks 5 through 8, of 30% for cytisinicline compared to 8% for placebo ($p= 0.005$). Smokers in the 3 mg TID arm had an odds ratio of 5.04 (95% CI: 1.42, 22.32) for continuous abstinence from week 5 to week 8, compared with placebo. The odds ratio, or OR, is a standard measure of association between an exposure (cytisinicline treatment) and an outcome (continuous smoking abstinence) such that in this study, smokers receiving 3 mg cytisinicline TID were 5 times more likely to stop smoking compared to subjects on placebo.

At week 4, all four cytisinicline arms demonstrated statistically significant ($p<0.05$) reductions in expired carbon monoxide, or CO, a biochemical measure of smoking activity. Expired CO levels had declined by a median of 71-80% in the cytisinicline treatment arms, compared to only 38% in the placebo arms. The greater reductions in expired CO levels for the cytisinicline arms versus placebo suggest that placebo-treated subjects may have over-reported their reduction in cigarettes smoked or overcompensated with greater inhalation while smoking fewer cigarettes.

Cytisinicline was well-tolerated with no serious adverse effects, or SAEs, reported. The most commonly reported (>5%) adverse effects, or AEs, across all cytisinicline treatment arms versus placebo arms were abnormal dreams, insomnia, upper respiratory tract infections, and nausea. In the 3 mg TID treatment arm versus placebo arms, the most common AEs were abnormal dreams, insomnia, and constipation (each 6% vs 2%), upper respiratory tract infections (6% vs 14%), and nausea (6% vs 10%), respectively. Compliance with study treatment was greater than 94% across all arms.

We presented the ORCA-1 results in September 2019 at the annual European meeting of the Society for Research on Nicotine and Tobacco, or SRNT, held in Oslo, Norway and the trial results were published in the journal Nicotine and Tobacco Research in April 2021. Based on the results of the ORCA-1 trial, we have selected 3 mg TID for Phase 3 development. Overall, the 3 mg dose administered TID demonstrated the best overall safety and efficacy when compared to the 1.5 mg dose or the declining titration schedule evaluated in ORCA-1. At the SRNT European meeting held in September 2021, exploratory analyses were presented that showed cytisinicline treatment had an earlier onset of sustained abstinence compared to placebo and that the cytisinicline TID schedule appeared more effective for achieving sustained abstinence in smokers who had previously failed to quit on varenicline compared to the declining titration schedule.

In November 2019, we held a type C meeting with the U.S. Food and Drug Administration, or FDA, to review the ORCA-1 results and our revisions to the Phase 3 clinical program using the simplified 3 mg TID dosing schedule. The FDA agreed that the 3 mg TID dosing schedule was acceptable.

Recently Completed Investigator-Sponsored Clinical Trial

In June 2020, we announced the topline results from the independent, investigator-sponsored Phase 3 RAUORA trial. RAUORA was a non-inferiority study comparing cytisinicline to Chantix (varenicline) in Māori (indigenous New Zealanders) and whānau (family) of Māori. The study was led by Dr. Natalie Walker, Associate Professor at the University of Auckland, and was funded by the Health Research Council of New Zealand. The study enrollment was planned for 2,140 subjects. In total, 1,105 Māori or whānau expressed interest in participating in the study and a total of 679 were randomized to receive either cytisinicline or varenicline. The average age of participants in the trial was 43 years and approximately 70% of the participants were women.

The study compared cytisinicline administered on a schedule of 25 days of declining titration followed by twice-daily dosing for a total of 12 weeks with varenicline administered on a schedule of seven days of inclining titration followed by twice-daily dosing for a total of 12 weeks. The primary endpoint was a comparison of biochemically confirmed continuous abstinence rates at 6 months, and the trial was designed to assess if the two agents were non-inferior to each other.

The primary endpoint of the non-inferiority trial was to demonstrate that cytisinicline quit rates would be no less than 10% lower than the quit rates for varenicline. Topline results indicated that the RAUORA trial achieved its primary endpoint in showing that cytisinicline plus behavioral support was at least as effective as varenicline plus behavioral support at 6 months. Cytisinicline met the pre-specified non-inferiority endpoint and was trending towards superiority with an Absolute Risk Difference of +4.29 in favor of cytisinicline (95% CI -0.22 to 8.79), demonstrating a 4.29% improvement in quit rates in favor of cytisinicline. Specifically, continuous abstinence rates at 6 months, verified by expired CO, were 12.1% for cytisinicline compared to 7.9% for varenicline. The Relative Risk was 1.55 on an intent-to-treat basis, indicating that subjects in the cytisinicline arm were approximately one and a half times more likely to have quit smoking at 6 months compared to subjects who received varenicline.

Additionally, significantly fewer overall AEs were reported in cytisinicline-treated subjects (Relative Risk 0.56, 95% CI 0.49 to 0.65, $p<0.001$). Notably, of the subjects who experienced adverse events, cytisinicline subjects reported significantly less nausea, insomnia and vivid dreams ($p<0.05$).

The final RAUORA trial results and additional analyses were presented at the SRNT European Annual Meeting in September 2020 and were published in the journal Addiction in March 2021. Also presented at the SRNT Europe Annual Meeting in September 2020 were results from a preclinical study conducted at the University of Cambridge Department of Biochemistry. The study was designed to examine the in vitro binding characteristics of cytisinicline compared to varenicline at the human 5-HT3 receptor. Using a radioligand antagonist displacement design, the study reported an IC50 of 0.50 mM for cytisinicline and 0.25 μM for varenicline, representing a 2000-greater fold agonist binding affinity to the 5-HT3 receptor for varenicline compared to cytisinicline. Agonist activation of 5-HT3 receptors in the brain stem has been shown to induce nausea and vomiting. The data demonstrating the difference in binding potency at the 5-HT3 receptor provide potential rationale for the lower overall incidence of adverse events reported for cytisinicline compared to varenicline.

Planned Company-Sponsored Phase 2 Clinical Trial

In July 2021, we announced that we were awarded a grant from the National Institute on Drug Abuse, or NIDA, of the National Institutes of Health, or NIH, to evaluate the use of cytisinicline as a treatment for cessation of nicotine e-cigarette use. This initial grant award, in the amount of $320,000, commenced on August 1, 2021, and is being utilized to complete critical regulatory and clinical operational activities, such as protocol finalization, clinical trial site identification, and submission of an Investigational New Drug Application, or IND, to the FDA for investigating cytisinicline in nicotine e-cigarette users. In November 2021, we announced that the FDA has completed their review and accepted the IND application to investigate cytisinicline as a cessation treatment in this population. Following NIH review of completed milestones, and subject to available NIH funding, we expect to receive the next stage of the grant award of approximately $2.5 million, which will enable initiation of the Phase 2 ORCA-V1 clinical study, which we anticipate to occur in the second quarter of 2022, to evaluate cytisinicline in approximately 150 adult nicotine e-cigarette users in the United States. The full grant award of $2.8 million is expected to cover approximately half of the ORCA-V1 clinical study costs. The Primary Investigators for the grant are our Chief Medical Officer, Dr. Cindy Jacobs, and Dr. Nancy Rigotti, Professor of Medicine at Harvard Medical School and Director, Tobacco Research and Treatment Center, Massachusetts General Hospital.

Non-clinical

Non-clinical toxicology studies were sponsored by the National Center for Complementary and Integrative Health, or NCCIH, a division of the NIH and by the National Cancer Institute, or NCI, to assist in our IND for investigating cytisinicline as a smoking cessation treatment. We filed this IND application for cytisinicline with the FDA in 2017, which included the NCCIH sponsored non-clinical studies. Additional NCCIH and NCI sponsored non-clinical toxicology studies were later submitted in support for initiating our Phase 3 program.

Non-clinical toxicology studies that will be required for a New Drug Application, or NDA, include two longer-term chronic toxicology studies and two carcinogenicity studies, which are in distinct stages of execution as company-sponsored studies. Two chronic toxicology studies have been completed and submitted to the FDA. Additionally, one of two carcinogenicity studies has been completed, while the second carcinogenicity study is currently in progress.

Impact of COVID-19 Pandemic

The extent of the impact of the COVID-19 pandemic on our operational and financial performance will depend on certain developments, including the duration of the outbreak, impact on our clinical studies, employee or industry events, and effect on our suppliers, service providers and manufacturers, all of which are uncertain and cannot be predicted. As a result of the COVID-19 pandemic, we may experience disruptions in our operations, liquidity, supply chain, facilities, and clinical trials. We may in the future experience more significant delays in enrollment, participant dosing, distribution of clinical trial materials, study monitoring and data analysis that could materially adversely impact our business, results of operations and overall financial performance in future periods. Specifically, we may experience impact from changes in how we and companies worldwide conduct business due to the COVID-19 pandemic, including but not limited to restrictions on travel and in-person meetings, delays in site activations and enrollment of clinical trials, prioritization of hospital resources toward pandemic effort, delays in review by the FDA, and disruptions in our supply chain for our product candidates. As of the filing date of this Annual Report on Form 10-K, the extent to which the COVID-19 pandemic has impacted our financial condition, results of operations or guidance has been minimal. The effect of any additional COVID-19 pandemic issues will not be fully reflected in our results of operations and overall financial performance until future periods. See the section titled “Risk Factors” for further discussion of the possible impact of the COVID-19 pandemic on our business.

Recent Corporate History

On July 29, 2020, we filed a certificate of amendment to our Second Amended and Restated Certificate of Incorporation, as amended, and effective as of July 31, 2020, for a 1-for-20 reverse stock split of our issued and outstanding shares of common stock. As a result of the reverse stock split, each 20 shares of the outstanding common stock were combined into one share of common stock without any change to the par value per share. The reverse stock split did not affect the number of authorized shares of common stock which remains at 150,000,000. The reverse stock split was approved by our board of directors and stockholders and was intended to allow us to regain compliance with the NASDAQ’s continued listing criteria related to the Minimum Bid Price Rule. On August 14, 2020, we received written confirmation from NASDAQ that we regained compliance with the Minimum Bid Price Rule and the matter was closed.

Unless otherwise noted, impacted amounts and share information included in the financial statements and notes thereto have been retroactively adjusted for the stock split as if such stock split occurred on the first day of the first period presented. Certain amounts in the notes to the financial statements may be slightly different than previously reported due to rounding of fractional shares as a result of the reverse stock split.

License & Supply Agreements

Sopharma License and Supply Agreements

We are party to a license agreement, or the Sopharma License Agreement, and a supply agreement, or the Sopharma Supply Agreement, with Sopharma, AD, or Sopharma. Pursuant to the Sopharma License Agreement, we were granted access to all available manufacturing, efficacy and safety data related to cytisinicline, as well as a granted patent in several European countries related to new oral dosage forms of cytisinicline providing enhanced stability. Additional rights granted under the Sopharma License Agreement include the exclusive use of, and the right to sublicense, certain cytisincline trademarks in all territories described in the Sopharma License Agreement. Under the Sopharma License Agreement, we agreed to pay a nonrefundable license fee. In addition, we agreed to make certain royalty payments equal to a mid-single digit percentage of all net sales of cytisinicline products in our territory during the term of the Sopharma License Agreement, including those sold by a third party pursuant to any sublicense which may be granted by us. To date, any amounts paid to Sopharma pursuant to the Sopharma License Agreement have been immaterial.

University of Bristol License Agreement

In July 2016, we entered into a license agreement with the University of Bristol, or the University of Bristol License Agreement. Under the University of Bristol License Agreement, we received exclusive and nonexclusive licenses from the University of Bristol to certain patent and technology rights resulting from research activities into cytisinicline and its derivatives, including a number of patent applications related to novel approaches to cytisinicline binding at the nicotinic receptor level.

In consideration of rights granted by the University of Bristol, we paid a nominal license fee and agreed to pay amounts of up to $3.2 million, in the aggregate, tied to a financing milestone and to specific clinical development and commercialization milestones resulting from activities covered by the University of Bristol License Agreement. Additionally, if we successfully commercialize any product candidates subject to the University of Bristol License Agreement, we are responsible for royalty payments in the low-single digits and payments up to a percentage in the mid-teens of any sublicense income, subject to specified exceptions, based upon net sales of such licensed products.

On January 22, 2018, we and the University of Bristol entered into an amendment to the University of Bristol License Agreement. Pursuant to the amended University of Bristol License Agreement we received exclusive rights for all human medicinal uses of cytisinicline across all therapeutic categories from the University of Bristol from research activities into cytisinicline and its derivatives. In consideration of rights granted by the amended University of Bristol License Agreement, we agreed to pay an initial amount of $37,500 upon the execution of the amended University of Bristol License Agreement, and additional amounts of up to $1.7 million, in the aggregate, tied to a financing milestone and to specific clinical development and commercialization milestones resulting from activities covered by the amended University of Bristol License Agreement, in addition to amounts under the original University of Bristol License Agreement of up to $3.2 million in the aggregate, tied to specific financing, development and commercialization milestones. Additionally, if we successfully commercialize any product candidate subject to the amended University of Bristol License Agreement or to the original University of Bristol License Agreement, we will be responsible, as provided in the original University of Bristol License Agreement, for royalty payments in the low-single digits and payments up to a percentage in the mid-teens of any sublicense income, subject to specified exceptions, based upon net sales of such licensed products. Up to December 31, 2021, we had paid the University of Bristol $125,000 pursuant to the University of Bristol License Agreement.

Research and Development Expenses

Research and development, or R&D, expenses consist primarily of costs for clinical trials, contract manufacturing, personnel costs, milestone payments to third parties, facilities, regulatory activities, non-clinical studies and allocations of other R&D-related costs. External expenses for clinical trials include fees paid to clinical research organizations, clinical trial site costs and patient treatment costs.

We manage our clinical trials through contract research organizations and independent medical investigators at our sites and at hospitals and expect this practice to continue. Due to our ability to utilize resources across several projects, we do not record or maintain information regarding the indirect operating costs incurred for our R&D programs on a program-specific basis. In addition, we believe that allocating costs on the basis of time incurred by our employees does not accurately reflect the actual costs of a project.

We expect our R&D expenses to increase for the foreseeable future as we continue to conduct our ongoing non-clinical studies, and initiate new clinical trials and registration-enabling activities. The process of conducting clinical trials and non-clinical studies necessary to obtain regulatory approval is costly and time consuming and we may never succeed in achieving marketing approval for cytisinicline. (See “Item 1A. Risk Factors—Risks Related to the Development of Our Product Candidate Cytisinicline.”)

Successful development of cytisinicline is highly uncertain and may not result in an approved product. We cannot estimate completion dates for development activities or when we might receive material net cash inflows from our R&D projects, if ever. We anticipate we will make determinations as to which markets, and therefore, which regulatory approvals, to pursue and how much funding to direct toward achieving regulatory approval in each market on an ongoing basis in response to our ability to enter into new strategic alliances with respect to each program or potential product candidate, the scientific and clinical success of each future product candidate, and ongoing assessments as to each future product candidate’s commercial potential. We will need to raise additional capital and may seek additional strategic alliances in the future in order to advance our various programs.

Our projects or intended R&D activities may be subject to change from time to time as we evaluate results from completed studies, our R&D priorities and available resources.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries and related costs for our personnel in executive, finance and accounting, corporate communications and other administrative functions, as well as consulting costs, including market research, business consulting, human resources and intellectual property. Other costs include professional fees for legal and auditing services, insurance and facility costs.

Results of Operations

Years Ended December 31, 2021, 2020 and 2019

Research and Development Expenses

Our research and development expenses for our clinical development programs were as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Clinical development programs:			
Cytisinicline	$ 23,966	$ 6,882	$ 9,674
Total research and development expenses	**$ 23,966**	**$ 6,882**	**$ 9,674**

Research and development expenses for the years ended December 31, 2021, 2020 and 2019 were $24.0 million, $6.9 million and $9.7 million, respectively. The increase in 2021 as compared to 2020 was primarily due to costs incurred as a result of the enrollment and ramp up of activity in our Phase 3 ORCA-2 trial that was initiated in the fourth quarter of 2020 and was fully enrolled by the middle of 2021. The decrease in 2020 as compared to 2019 was primarily due to the timing of our completion of the ORCA-1 trial, a Phase 2b optimization study that was initiated in October 2018 and completed in June 2019, and the initiation of the ORCA-2 trial in October 2020.

General and Administrative Expenses

Our general and administrative expenses were as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Total general and administrative expenses	**$ 9,128**	**$ 7,868**	**$ 6,854**

G&A expenses for the years ended December 31, 2021, 2020 and 2019 were $9.1 million, $7.9 million, and $6.9 million, respectively. The increase in 2021 as compared to 2020 was primarily due to higher employee expenses associated with stock-based compensation, and increases in premiums for insurance and clinical trial media and awareness expenses. The increase in 2020 as compared to 2019 was primarily due to higher employee costs, increased activity on patent development, additional market research and public relations activities, and increased insurance premiums. This was partially offset by lower travel costs as a result of travel restrictions across the United States and other countries during the COVID-19 pandemic.

Liquidity and Capital Resources

We have incurred an accumulated deficit of $93.6 million through December 31, 2021 and we expect to incur substantial additional losses in the future as we operate our business and continue or expand our R&D activities and other operations. We have not generated any revenue from product sales to date, and we may not generate product sales revenue in the near future, if ever. As of December 31, 2021, we had a cash and cash equivalents balance of $43.0 million and a positive working capital balance of $40.0 million. We believe that our existing cash, cash equivalents and restricted cash, will be sufficient for us to fund our current operating expenses and capital expenditures into 2023.

We have historically financed our operations through equity and debt financings. While we believe that we will be able to settle our commitments and liabilities in the normal course of business as they fall due during the next 12 months, as a development-stage company with no current sources of revenue, our ability to support our working capital and capital expenditure requirements in the long term will depend on many factors, including our ability to raise funds (through public or private securities offerings, debt financings, government funding or grants, or other sources, which may include licensing, collaborations or other strategic transactions or arrangements) to support the ongoing advancement of our clinical trials and corporate activities.

We did not have during the periods presented, and we do not currently have, any commitments or obligations, including contingent obligations, arising from arrangements with unconsolidated entities or persons that have or are reasonably likely to have a material current or future effect on our financial condition, changes in financial condition, revenues or expenses, results of operations, liquidity, cash requirements or capital resources.

Lincoln Park Capital Equity Line

On September 14, 2017, we and Lincoln Park Capital Fund, LLC, or LPC, entered into a share and unit purchase agreement, which was amended on March 12, 2020, or the Purchase Agreement, pursuant to which we have the right to sell to LPC up to $11.0 million in shares of our common stock, par value $0.001 per share, subject to certain limitations and conditions set forth in the Purchase Agreement. On May 22, 2018 we obtained the requisite stockholder authorization to sell shares of our common stock to LPC in excess of 20% of our outstanding shares of common stock (as of the date we entered into the Purchase Agreement) in order to be able to sell to LPC the full amount remaining under the Purchase Agreement.

Pursuant to the Purchase Agreement, LPC initially purchased 1,644 of our units, or the Units, at a purchase price of $608.00 per unit, with each Unit consisting of (a) one share of our common stock and (b) one warrant to purchase one-quarter of a share of common stock at an exercise price of $699.20 per share, or Warrant. Each Warrant became exercisable six months following the issuance date until the date that is five years and six months after the issuance date and is subject to customary adjustments. The Warrants were issued only as part of the Units in the initial purchase of $1.0 million and no warrants shall be issued in connection with any other purchases of common stock under the Purchase Agreement.

After the initial purchase, if our stock price is above $1.00, as often as every other business day over the 54-month term of the Purchase Agreement, and up to an aggregate amount of an additional $10.0 million (subject to certain limitations) of shares of common stock, we have the right, from time to time, in our sole discretion and subject to certain conditions to direct LPC to purchase up to 7,500 shares of common stock. The purchase price of shares of common stock pursuant to the Purchase Agreement will be based on prevailing market prices of common stock at the time of sales without any fixed discount, and we will control the timing and amount of any sales of common stock to LPC. As consideration for entering into the Purchase Agreement, we issued to LPC 617 shares of common stock in September 2017 and, in connection with the amendment of the Purchase Agreement in March 2020, we paid to LPC $0.1 million as an expense reimbursement. The consideration of 617 shares of our common stock were fair valued based on the closing price of our common stock as at the transaction date and recognized as part of offering expenses.

During the year ended December 31, 2021, we offered and sold zero shares of our common stock pursuant to the Purchase Agreement with LPC. Since entry into the Purchase Agreement, from September 14, 2017 through March 10, 2022, we offered and sold an aggregate of 27,868 shares of our common stock, including the 1,644 shares that were part of the initial purchase of Units. These aggregate sales resulted in gross proceeds to us of approximately $4.4 million and offering expenses of $0.5 million. The purchase agreement will expire on March 14, 2022.

April 2020 Private Placement

On April 27, 2020 and April 28, 2020, we entered into subscription agreements with certain accredited investors pursuant to which we sold to the purchasers in a private placement approximately 280,782 units, or Units, each consisting of (i) one share of common stock,

and (ii) a warrant to purchase 0.75 shares of common stock at an offering price of $6.60 per Unit, for aggregate gross proceeds of approximately $1.9 million. The placement agent for the offering received a cash commission on the gross proceeds from the sale of the Units and was issued a five year warrant upon substantially similar terms as the investors' warrants to purchase 25,270 shares of common stock at an initial exercise price of $7.59 per share. The net proceeds to us, after deducting placement agent expenses and commissions and offering expenses was approximately $1.6 million.

Each warrant became exercisable on October 27, 2020, the six-month anniversary of the initial closing date of the offering, through April 27, 2025, which is the five-year anniversary of the initial closing date of the offering. The warrants issued pursuant to subscription agreements executed on April 27, 2020 are exercisable at a price per share of common stock of $7.24, subject to adjustment, and the warrants issued pursuant to subscription agreements executed on April 28, 2020 are exercisable at a price per share of common stock of $7.32, subject to adjustment. Additionally, subject to certain exceptions, if, after the initial exercise date, (i) the volume weighted average price of the common stock for each of 30 consecutive trading days, or the Measurement Period, which, Measurement Period commences on the closing date, exceeds 300% of the exercise price (subject to adjustments for stock splits, recapitalizations, stock dividends and similar transactions), (ii) the average daily trading volume for such Measurement Period exceeds $500,000 per trading day and (iii) certain other equity conditions are met, and subject to a beneficial ownership limitation, then we may call for cancellation of all or any portion of the warrants then outstanding.

July 2020 Registered Direct Offering

On July 1, 2020, we completed a registered direct offering, pursuant to which we sold 731,707 shares of our common stock at a price of $8.20 per share.

The registered direct offering raised total gross proceeds of approximately $6.0 million, and after deducting approximately $0.7 million in placement agent fees and offering expenses, we received net proceeds of approximately $5.3 million.

August 2020 Public Offering

On August 6, 2020, we completed an underwritten public offering of our securities, pursuant to which we sold an aggregate of (a) 569,043 shares of our common stock, including 92,856 shares subject to the underwriter's option to purchase additional shares, or the August Shares, and (b) pre-funded warrants to purchase 142,857 shares of our common stock, or the Pre-Funded Warrants, to the underwriter. The August Shares were sold at the public offering price of $10.50 per share. The Pre-Funded Warrants were sold at a public offering price of $10.499 per Pre-Funded Warrant, which represents the per share public offering price for the August Shares less a $0.001 per share exercise price for each such Pre-Funded Warrant.

The Pre-Funded Warrants are exercisable at any time after the date of issuance. A holder of Pre-Funded Warrants may not exercise the warrant if the holder, together with its affiliates, would beneficially own more than 9.99% of the number of shares of common stock outstanding immediately after giving effect to such exercise. A holder of Pre-Funded Warrants may increase or decrease this percentage, but not in excess of 19.99%, by providing at least 61 days' prior notice to us.

The underwritten public offering raised total gross proceeds of approximately $7.5 million and after deducting approximately $0.7 million in underwriting discounts and commissions and offering expenses, we received net proceeds of approximately $6.8 million. The underwriting discounts and commissions and offering expenses have been charged against the gross proceeds.

December 2020 Public Offering

On December 7, 2020, we completed an underwritten public offering of our securities, pursuant to which we sold an aggregate of 2,472,500 shares of our common stock, including 322,500 shares subject to the underwriter's option to purchase additional shares, or the December Shares. The December Shares were sold at the public offering price of $7.00 per share.

We also issued a warrant to purchase 50,000 shares of common stock to the representative of the underwriters, or the Representative's Warrant, as a portion of the underwriting compensation payable in connection with this offering. The Representative's Warrant will be exercisable beginning on May 31, 2021, with an exercise price of $8.75 per share and a term of five years. Under ASC 260, the fair value of the Representative's Warrant of $0.3 million was charged against Additional Paid-In Capital.

The underwritten public offering raised total gross proceeds of approximately $17.3 million and after deducting approximately $1.5 million in underwriting discounts and commissions and offering expenses, we received net proceeds of approximately $15.8 million. The underwriting discounts and commissions and offering expenses have been charged against the gross proceeds.

May 2021 Public Offering

On May 27, 2021, we completed an underwritten public offering of our securities, pursuant to which we sold an aggregate of 3,285,714 shares of our common stock, including 428,571 shares subject to the underwriter's option to purchase additional shares, or the May Shares. The May Shares were sold at the public offering price of $7.00 per share.

The underwritten public offering raised total gross proceeds of approximately $23.0 million and after deducting approximately $1.7 million in underwriting discounts and commissions and offering expenses, we received net proceeds of approximately $21.3 million. The underwriting discounts and commissions and offering expenses have been charged against the gross proceeds.

December 2021 Convertible Debt

On December 22, 2021, we entered into a $25.0 million contingent convertible debt agreement, or Debt Agreement, with Silicon Valley Bank, or SVB, and SVB Innovation Credit Fund VIII, L.P., or, together with SVB, the Lenders. As part of the contingent convertible debt agreement, the Lenders funded $15.0 million in the form of convertible indebtedness, or Convertible Debt, at closing. Subject to certain terms and conditions, we may borrow additional non-convertible term loans in an aggregate original principal amount of up to $10.0 million.

Under the terms of the agreement, the Convertible Debt matures on December 22, 2023 and may be extended to December 22, 2024 upon our written request and SVB's approval on or prior to December 22, 2023. The Convertible Debt will accrue interest at the aggregate of (a) a floating rate per annum equal to the greater of (i) 2.25% and (ii) the prime rate minus 1.0%, which interest is payable in cash monthly in arrears, and (b) 7.0% per annum, which interest shall compound monthly.

Subject to certain terms and conditions, the Lenders may convert all or any part of the outstanding Convertible Debt and accrued and unpaid interest at any time prior to maturity into shares of our common stock at a conversion price equal to $9.34 per share, subject to customary anti-dilution adjustments. Additionally, all outstanding Convertible Debt, including accrued and unpaid interest, will mandatorily convert into shares of our common stock, at the conversion price, on such date, if any, when the closing price per share of our common stock has been equal to or greater than $24.00 for 30 consecutive trading days prior to such date.

We have the right, or Call Right, at any time to repay and retire all (but not less than all) of the outstanding Convertible Debt and accrued and unpaid interest, if any, prior to its conversion by payment of a premium determined based on the date of such repayment equal to:

- 125% of the principal amount of the Convertible Debt including accrued paid-in-kind interest, or PIK, if the Call Right is exercised on or before the 18-month anniversary of the date of the Debt Agreement; and
- 150% of the principal amount of the Convertible Debt including accrued PIK, if the Call Right is exercised after the 18-month anniversary of the date of the Debt Agreement,

in either case together with all accrued and unpaid interest on the principal balance of the Convertible Debt. If the Call Right is exercised by us, the Lenders will retain certain lookback rights in the event we enter into an agreement to be acquired in the 12 months following the exercise of the Call Right. We agreed to grant the Lenders a security interest in virtually all of our assets, including our patents and other intellectual property as security for our obligations under the Debt Agreement.

At-the-Market Sales Agreement

On December 21, 2022, we entered into an At-the-Market Offering Sales Agreement, or ATM, with Virtu Americas, LLC, as sales agent, pursuant to which we may sell shares of common stock with an aggregate offering price of up to $25 million. During the year ended December 31, 2021, we did not sell any shares under the ATM. As of December 31, 2021, we had $25.0 million available in our ATM.

Cash Flows

Operating Activities

For the years ended December 31, 2021, 2020 and 2019, net cash used in operating activities was $29.4 million, $13.5 million, and $15.2 million, respectively. The increase in cash used in operations in 2021 as compared to 2020 was primarily due to an increase in research and development expenses related to our ORCA-2 trial. The decrease in cash used in operations in 2020 as compared to 2019

was primarily attributable to a decrease in research and development expenses related to our ORCA-1 trial, which was partially offset by expenses incurred in connection with the initiation of the ORCA-2 trial in October 2020.

Financing Activities

For the years ended December 31, 2021, 2020 and 2019 net cash provided by financing activities was $36.6 million, $32.7 million and $17.3 million, respectively. Net cash provided by financing activities for the year ended December 31, 2021 relates to proceeds received from our May 2021 public offering, December 2021 convertible debt financing and warrant exercises. Net cash provided by financing activities for the year ended December 31, 2020 relates to proceeds from our December 2020 public offering, August 2020 public offering, July 2020 registered direct offering, from warrant exercises and from our April 2020 private placement. Net cash provided by financing activities for the year ended December 31, 2019 relates to proceeds from our December 2019 public offering, from warrant exercises and from our purchase agreement with LPC.

Investing Activities

There were no investing activities in 2021. Net cash used in investing activities for the year ended December 31, 2020 was $17,000 and was attributable to the purchase of equipment. Net cash provided by investing activities for the year ended December 31, 2019 was $5.0 million and was due mainly to transactions involving short-term investments in the normal course of business.

Critical Accounting Policies and Estimates

Use of Estimates

The preparation of consolidated financial statements in conformity with U.S. generally accepted accounting principles requires management to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and notes thereto. Actual results could differ from these estimates. Estimates and assumptions principally relate to estimates of the initial fair value and forfeiture rates of stock options issued to employees and consultants, the estimated compensation cost on performance restricted stock unit awards, clinical trial and manufacturing accruals, estimated useful lives of property, plant, equipment and intangible assets, estimates and assumptions in contingent liabilities.

Intangible Assets

Our intangible assets are subject to amortization and are amortized using the straight-line method over their estimated period of benefit. We evaluate the carrying amount of intangible assets periodically by taking into account events or circumstances that may warrant revised estimates of useful lives or that indicate the asset may be impaired.

Impairment of Long-Lived Assets

We review long-lived assets for impairment whenever events or changes in circumstances indicate that the asset's carrying amount may not be recoverable. We conduct our long-lived asset impairment analyses in accordance with ASC 360-10-15, "Impairment or Disposal of Long-Lived Assets." ASC 360-10-15 requires us to group assets and liabilities at the lowest level for which identifiable cash flows are largely independent of the cash flows of other assets and liabilities and evaluate the asset group against the sum of the undiscounted future cash flows. If the undiscounted cash flows do not indicate the carrying amount of the asset is recoverable, an impairment charge is measured as the amount by which the carrying amount of the asset group exceeds its fair value based on discounted cash flow analysis or appraisals.

Goodwill

Goodwill acquired in a business combination is assigned to the reporting unit that is expected to benefit from the combination as of the acquisition date. Goodwill is tested for impairment on an annual basis or, more frequently, if an event occurs or circumstances change that would more likely than not reduce the fair value of the reporting unit.

Government Grants

We account for government grants by recognizing the benefit of the grant as qualifying expenditures are incurred provided that there is reasonable assurance that we have complied with all conditions under the terms of the grant and that the amount requested for reimbursement will be received. The government grant reduces the research and development expenses to which it relates on our statement of profit and loss.

Research and Development Costs

Research and development costs are expensed as incurred, net of related refundable investment tax credits, with the exception of non-refundable advance payments for goods or services to be used in future research and development, which are capitalized in accordance with ASC 730, "Research and Development" and included within Prepaid Expenses or Other Assets depending on when the assets will be utilized.

Clinical trial expenses are a component of research and development costs. These expenses include fees paid to contract research organizations and investigators and other service providers, which conduct certain product development activities on our behalf. We use an accrual basis of accounting, based upon estimates of the amount of service completed. In the event payments differ from the amount of service completed, prepaid expense or accrued liabilities amounts are adjusted on the balance sheet. These expenses are based on estimates of the work performed under service agreements, milestones achieved, patient enrollment and experience with similar contracts. We monitor each of these factors to the extent possible and adjust estimates accordingly.

Stock-Based Compensation

Under the fair value recognition provisions of the ASC 718, "Stock Compensation", we use the modified prospective method with respect to options granted to employees and directors. The expense is amortized on a straight-line basis over the graded vesting period.

Restricted Stock Unit Awards

We grant restricted stock unit awards that generally vest and are expensed over a four-year period. We also granted restricted stock unit awards that vest in conjunction with certain performance conditions to certain executive officers and key employees. At each reporting date, we evaluate whether achievement of the performance conditions is probable. Compensation expense is recorded over the appropriate service period based upon our assessment of accomplishing each performance provision or the occurrence of other events that may have caused the awards to accelerate and vest.

Warrants

We account for warrants pursuant to the authoritative guidance on accounting for derivative financial instruments indexed to, and We account for warrants pursuant to the authoritative guidance on accounting for derivative financial instruments indexed to, and potentially settled in, a company's own stock, on the understanding that in compliance with applicable securities laws, the warrants require the issuance of registered securities upon exercise and therefore do not sufficiently preclude an implied right to net cash settlement. We have warrants classified as equity and these are not reassessed for their fair value at the end of each reporting period. Warrants classified as equity are initially measured at their fair value and recognized as part of stockholders' equity. Determining the appropriate fair-value model and calculating the fair value of registered warrants requires considerable judgment, including estimating stock price volatility and expected warrant life. The computation of expected volatility was based on the historical volatility of comparable companies from a representative peer group selected based on industry and market capitalization. A small change in the estimates used may have a relatively large change in the estimated valuation. We use the Black-Scholes pricing model to value the warrants.

Recently Adopted Accounting Policies

In February 2016, the FASB established Topic 842, Leases, by issuing Accounting Standards Update ASU No. 2016-02, which requires lessees to recognize leases on-balance sheet and disclose key information about leasing arrangements. The new standard establishes a right-of-use, or ROU, model that requires a lessee to recognize a ROU asset and lease liability on the balance sheet for all leases with a term longer than 12 months. Leases were classified as finance or operating, with classification affecting the pattern and classification of expense recognition in the consolidated statements of loss and comprehensive loss.

We adopted the standard on the effective date of January 1, 2019 and elected to use the modified retrospective method. Consequently, financial information will not be updated and the disclosures required under the new standard will not be provided for dates and periods before January 1, 2019. We elected the short-term lease recognition exemption for all leases that qualify. This means, for those leases that qualify, we will not recognize ROU assets or lease liabilities, and this includes not recognizing ROU assets or lease liabilities for existing

short-term leases of those assets in transition. We also elected the available practical expedients and implemented internal controls to enable the preparation of financial information on adoption.

The standard had a material impact on our consolidated balance sheets, but did not have an impact on our consolidated statements of loss and comprehensive loss. The most significant impact was the recognition of ROU assets and lease liabilities for operating leases, while our accounting for finance leases remained substantially unchanged.

In August 2018, the FASB issued Accounting Standards Update 2018-13, Fair Value Measurement, which both modifies and clarifies the disclosure requirements for fair value measurement. This update is effective for financial statements issued for fiscal years beginning after December 15, 2019, with early adoption permitted. The adoption of this standard did not have a significant impact on our financial position or results of operations.

In August 2020, the FASB issued Accounting Standards Update No. 2020-06, Debt – Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging – Contracts in Entity's Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity's Own Equity, or ASU 2020-06. ASU 2020-06 simplifies the accounting for convertible instruments, the accounting for contracts in an entity's own equity, and the related earnings per share calculations. The new standard is effective for fiscal years beginning after December 15, 2021 and early adoption is permitted as of the beginning of an interim period for which financial statements (interim or annual) have not been issued or have not been made available for issuance.

We elected to early adopt the standard effective in 2021. The adoption of this standard did not have any impact on our prior period financial statements.

As a result of adopting ASU 2020-06, we are not required to separately record the conversion feature of the convertible debt but instead account for the convertible instrument and conversion feature as a single unit of debt.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

Not applicable.

TEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

INDEX TO FINANCIAL STATEMENTS:

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Board of Directors and Stockholders of Achieve Life Sciences, Inc.

To the Board of Directors and Stockholders of Achieve Life Sciences, Inc.

Opinion on the Financial Statements

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

Basis for Opinion

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

We conducted our audits of these consolidated financial statements in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud. 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 consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matters

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

Liquidity

As described in Note 1 to the consolidated financial statements, the Company has historically experienced recurring losses from operations. As of December 31, 2021, the Company had cash and cash equivalents of $43.0 million and a positive working capital balance of $40.0 million. During the year ended December 31, 2021, the Company incurred a net loss of $33.2 million and net cash used in operating activities was $29.4 million. The Company believes that it will be able to settle its commitments and liabilities in the normal course of business as they fall due for at least twelve months from the date of issuance of the financial statements. As a development stage company with no current sources of revenue, the Company is dependent on its ability to raise funds (through public or private securities offerings, debt financings, government funding or grants, or other sources, which may include licensing, collaborations or other strategic transactions or arrangements) to support the ongoing advancement of its clinical trials and corporate activities.

The principal considerations for our determination that performing procedures relating to liquidity is a critical audit matter are the significant judgments required by management in developing assumptions related to the amount and timing of future funding requirements, including the pace and results of clinical development efforts, which led to auditor judgment and subjectivity in performing procedures to evaluate management's future funding requirements.

Addressing the matter involved performing procedures and evaluating audit evidence in connection with forming our overall opinion on the consolidated financial statements. These procedures included, among others, evaluating the appropriateness of management's assessment of the Company's liquidity position. This assessment included evaluating the reasonableness of assumptions used in developing the amount and timing of future funding requirements, which include the pace and results of clinical development efforts. The evaluation of assumptions considered the past performance of the Company and consistency with evidence obtained in other areas of the audit. Additionally, these procedures included evaluating the sufficiency of the Company's liquidity disclosure.

PricewaterhouseCoopers LLP (signed)

Chartered Professional Accountants
Vancouver, Canada
March 10, 2022

We have served as the Company's auditor since 2017.

Achieve Life Sciences, Inc.

Consolidated Balance Sheets

(In thousands, except per share and share amounts)

	December 31, 2021	December 31, 2020
ASSETS		
Current assets:		
Cash and cash equivalents *[note 7]*	$ 43,022	$ 35,853
Grant receivable *[note 4]*	153	—
Prepaid expenses and other assets	1,419	1,122
Total current assets	**44,594**	**36,975**
Other assets and restricted cash *[note 7, note 8 and note 9]*	183	279
Right-of-use assets *[note 13]*	64	146
License agreement *[note 5 and 6]*	1,641	1,864
Goodwill *[note 5]*	1,034	1,034
Total assets	**$ 47,516**	**$ 40,298**
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 841	$ 332
Accrued liabilities other	348	584
Accrued clinical liabilities	1,352	453
Accrued compensation	1,940	1,474
Current portion of long-term obligations *[note 13]*	69	92
Total current liabilities	**4,550**	**2,935**
Convertible debt *[note 10]*	14,920	—
Long-term obligations *[note 13]*	4	77
Total liabilities	**19,474**	**3,012**
Commitments and contingencies *[note 13]*		
Stockholders' equity:		
Series A convertible preferred stock, $0.001 par value, 9,158 shares designated, zero issued and outstanding at December 31, 2021 and December 31, 2020.	—	—
Series B convertible preferred stock, $0.001 par value, 6,256 shares designated, zero issued and outstanding at December 31, 2021 and December 31, 2020.	—	—
Common stock, $0.001 par value, 150,000,000 shares authorized, 9,453,542 and 6,111,735 issued and outstanding at December 31, 2021 and December 31, 2020, respectively.	79	76
Additional paid-in capital	121,545	97,640
Accumulated deficit	(93,586)	(60,434)
Accumulated other comprehensive income	4	4
Total stockholders' equity	**28,042**	**37,286**
Total liabilities and stockholders' equity	**$ 47,516**	**$ 40,298**

See accompanying notes.

Achieve Life Sciences, Inc.

Consolidated Statements of Loss and Comprehensive Loss

(In thousands, except per share and share amounts)

	Year Ended December 31,		
	2021	2020	2019
EXPENSES			
Research and development	$ 23,966	$ 6,882	$ 9,674
General and administrative	9,128	7,868	6,854
Total operating expenses	33,094	14,750	16,528
OTHER INCOME (EXPENSE)			
Interest income	17	69	170
Other expenses	(75)	(49)	(37)
Total other income (expense)	(58)	20	133
Net loss and comprehensive loss	$ (33,152)	$ (14,730)	$ (16,395)
Basic and diluted net loss per common share *[note 1 and note 12 [g]]*	$ (4.08)	$ (5.42)	$ (39.76)
Shares used in computation of basic and diluted net loss per common share *[note 1 and note 12 [g]]*	8,119,836	2,718,909	412,320

See accompanying notes.

Achieve Life Sciences, Inc.

Consolidated Statements of Stockholders' Equity

(In thousands, except share amounts)

	Common Stock		Preferred Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total, Stockholders' Equity
	Shares	Amount	Shares	Amount				
Balance, December 31, 2018	336,055	18	579	—	41,161	4	(25,381)	15,802
Stock-based compensation expense	—	—	—	—	1,201	—	—	1,201
Restricted stock unit settlements	254	—	—	—	—	—	—	—
Adjustments to final October 2018 financing costs	—	—	—	—	4	—	—	4
Cumulative adjustment on adoption of lease standard	—	—	—	—	—	—	(3)	(3)
Shares issued - from purchase agreement with Lincoln Park Capital	18,700	—	—	—	792	—	—	792
Shares issued - December 2019 Public offering	628,876	13	6,256	—	12,321	—	—	12,334
Adjustments to final June 2018 financing costs	—	—	—	—	116	—	—	116
Shares issued on exercise of warrants	55,390	1	—	—	4,198	—	—	4,199
Shares issued on conversion of Series A preferred shares	7,237	—	(579)	—	—	—	—	—
Shares issued on conversion of Series B preferred shares	427,746	9	(5,135)	—	(9)	—	—	—
Issuance of inducement warrants	—	—	—	—	3,925	—	(3,925)	—
Net loss	—	—	—	—	—	—	(16,395)	(16,395)
Balance, December 31, 2019	1,474,258	41	1,121	—	63,709	4	(45,704)	18,050
Stock-based compensation expense	—	—	—	—	1,286	—	—	1,286
Costs relating to purchase agreement with Lincoln Park Capital	—	—	—	—	(14)	—	—	(14)
Shares issued on exercise of warrants	489,947	7	—	—	3,224	—	—	3,231
Shares issued - April 2020 Private placement	280,782	6	—	—	1,573	—	—	1,579
Shares issued - July 2020 Registered direct offering	731,707	15	—	—	5,292	—	—	5,307
Shares issued - August 2020 Public offering	569,043	1	—	—	6,821	—	—	6,822
Shares issued - December 2020 Public offering	2,472,500	2	—	—	15,787	—	—	15,789
Restricted stock unit settlements	128	—	—	—	—	—	—	—
Costs relating to December 2019 Public offering	—	—	—	—	(34)	—	—	(34)
Shares issued on conversion of Series A preferred shares	—	2	—	—	(2)	—	—	—
Shares issued on conversion of Series B preferred shares	93,379	2	(1,121)	—	(2)	—	—	—
Adjustment of fractional shares on reverse stock split	(9)	—	—	—	—	—	—	—
Net loss	—	—	—	—	—	—	(14,730)	(14,730)

Balance, December 31, 2020	6,111,735	76	—	—	97,640	4	(60,434)	37,286
Stock-based compensation expense		—	—	—	2,187	—	—	2,187
Shares issued on exercise of warrants	50,834	—	—	—	338	—	—	338
Shares issued as settlement with trade vendor	5,114	—	—	—	41	—	—	41
Shares issued - May 2021 public offering	3,285,714	3	—	—	21,340	—	—	21,343
Restricted stock unit settlements	145	—	—	—	(1)	—	—	(1)
Net loss	—	—	—	—	—	—	(33,152)	(33,152)
Balance, December 31, 2021	9,453,542	79	—	—	121,545	4	(93,586)	28,042

See accompanying notes.

Achieve Life Sciences, Inc.

Consolidated Statements of Cash Flows

(In thousands)

	Year Ended December 31,		
	2021	2020	2019
Operating Activities:			
Net loss	$ (33,152)	$ (14,730)	$ (16,395)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation	27	32	31
Amortization *[note 5]*	223	223	223
Stock-based compensation *[note 12[c]]*	2,187	1,286	1,201
Shares issued as settlement with trade vendor	41	—	—
Cumulative adjustment on adoption of lease standard	—	—	(3)
Changes in operating assets and liabilities:			
Grant receivable *[note 4]*	(153)	—	—
Prepaid expenses and other assets	(228)	(452)	194
Accounts payable	509	(527)	715
Accrued liabilities other	(245)	280	(328)
Accrued clinical liabilities	899	66	(812)
Accrued compensation	466	358	(52)
Lease obligation	(14)	(10)	10
Net cash used in operating activities	(29,440)	(13,474)	(15,216)
Financing Activities:			
Proceeds from purchase agreement with Lincoln Park Capital, net of issuance costs	—	—	792
Financing costs relating to purchase agreement with Lincoln Park Capital	—	(14)	—
Proceeds from exercise of warrants	338	3,231	4,199
Proceeds from December 2019 public offering, net of issuance costs	—	—	12,334
Financing costs relating to the December 2019 public offering	—	(34)	—
Proceeds from the April 2020 private placement, net of issuance costs	—	1,579	—
Proceeds from the July 2020 registered direct offering, net of issuance costs	—	5,307	—
Proceeds from the August 2020 public offering, net of issuance costs	—	6,822	—
Proceeds from the December 2020 public offering, net of issuance costs	—	15,789	—
Proceeds from the May 2021 public offering, net of issuance costs	21,343	—	—
Receipt of convertible debt from SVB *[note 10]*	14,929	—	—
Net cash provided by financing activities	36,610	32,680	17,325
Investing Activities:			
Purchase of property and equipment	—	(17)	(53)
Purchase of investments	—	—	(25)
Maturities of investments	—	—	5,114
Net cash provided by (used in) investing activities	—	(17)	5,036
Effect of exchange rate changes on cash	(1)	—	4
Net increase (decrease) in cash, cash equivalents and restricted cash	7,169	19,189	7,149
Cash, cash equivalents and restricted cash at beginning of year	35,903	16,714	9,565
Cash, cash equivalents and restricted cash at end of year	$ 43,072	$ 35,903	$ 16,714

See accompanying notes.

1. NATURE OF BUSINESS, BASIS OF PRESENTATION AND LIQUIDITY RISK

Achieve Life Sciences, Inc. (referred to as "Achieve," "we," "us," or "our") is a clinical-stage pharmaceutical company committed to the global development and commercialization of cytisinicline for smoking cessation. We were incorporated in the state of Delaware, and our principal executive office is located in Vancouver, British Columbia.

Liquidity

We have historically experienced recurring losses from operations that have incurred an accumulated deficit of $93.6 million through December 31, 2021. At December 31, 2021, we had cash and cash equivalents of $43.0 million and a positive working capital balance of $40.0 million. During the year ended December 31, 2021, we incurred a net loss of $33.2 million and net cash used in operations was $29.4 million. We have historically financed our operations through equity and debt financings. While we believe that we will be able to settle our commitments and liabilities in the normal course of business as they fall due during the next 12 months, as a development-stage company with no current sources of revenue, we are dependent on our ability to raise funds (through public or private securities offerings, debt financings, government funding or grants, or other sources, which may include licensing, collaborations or other strategic transactions or arrangements) to support the ongoing advancement of our clinical trials and corporate activities.

Reverse Stock Split

On July 29, 2020, we filed a certificate of amendment to our Second Amended and Restated Certificate of Incorporation, as amended, and effected as of July 31, 2020 a 1-for-20 reverse stock split of our issued and outstanding shares of common stock. As a result of the reverse stock split, each 20 shares of the outstanding common stock were combined into one share of common stock without any change to the par value per share. The reverse stock split did not affect the number of authorized shares of common stock which remains at 150,000,000. The reverse stock split was approved by our board of directors and stockholders and is intended to allow us to regain compliance with the NASDAQ's continued listing criteria related to the Minimum Bid Price Rule. On August 14, 2020, we received written confirmation from NASDAQ that we regained compliance with the Minimum Bid Price Rule and the matter has been closed.

Unless otherwise noted, impacted amounts and share information included in the financial statements and notes thereto have been retroactively adjusted for the stock split as if such stock split occurred on the first day of the first period presented. Certain amounts in the notes to the financial statements may be slightly different than previously reported due to rounding of fractional shares as a result of the reverse stock split.

Basis of Presentation

The consolidated financial statements include the accounts of Achieve and our wholly owned subsidiaries, Achieve Life Sciences Technologies Inc., Achieve Life Science, Inc., Extab Corporation, and Achieve Pharma UK Limited. All intercompany balances and transactions have been eliminated.

2. ACCOUNTING POLICIES

Significant Accounting Policies

Use of Estimates

The preparation of consolidated financial statements in conformity with United States generally accepted accounting principles requires management to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and notes thereto. Actual results could differ from these estimates. Estimates and assumptions principally relate to estimates of the initial fair value and forfeiture rates of stock options issued to employees and consultants, the estimated compensation cost on performance restricted stock unit awards, clinical trial and manufacturing accruals, estimated useful lives of property, plant, equipment and intangible assets, estimates and assumptions in contingent liabilities.

Cash Equivalents

We consider all highly liquid investments with an original maturity ofthree months or less to be cash equivalents, which we consider as available for sale and carry at fair value, with unrealized gains and losses, if any, reported as accumulated other comprehensive income or loss, which is a separate component of stockholders' equity.

Fair value of financial instruments

Other financial instruments including accounts payable, accrued liabilities other, accrued clinical liabilities and accrued compensation are carried at cost, which we believe approximates fair value because of the short-term maturities of these instruments.

Intellectual Property

The costs of acquiring intellectual property rights to be used in the research and development process, including licensing fees and milestone payments, are charged to research and development expense as incurred in situations where we have not identified an alternative future use for the acquired rights, and are capitalized in situations where we have identified an alternative future use. No costs associated with acquiring intellectual property rights have been capitalized to date. Costs of maintaining intellectual property rights are expensed as incurred.

Intangible Assets

Our intangible assets are subject to amortization and are amortized using the straight-line method over their estimated period of benefit. We evaluate the carrying amount of intangible assets periodically by taking into account events or circumstances that may warrant revised estimates of useful lives or that indicate the asset may be impaired.

Goodwill

Goodwill acquired in a business combination is assigned to the reporting unit that is expected to benefit from the combination as of the acquisition date. Goodwill is tested for impairment on an annual basis or, more frequently, if an event occurs or circumstances change that would more likely than not reduce the fair value of the reporting unit.

Property and Equipment

Property and equipment assets are recorded at cost less accumulated depreciation. Depreciation expense on assets acquired under capital lease is recorded within depreciation expense. Depreciation is recorded on a straight-line basis over the following periods:

Computer equipment	3 years
Furniture and fixtures	5 years
Machinery and equipment	5 - 10 years
Leasehold improvements and equipment under capital lease	Over the term of the lease

Impairment of Long-Lived Assets

We review long-lived assets for impairment whenever events or changes in circumstances indicate that the asset's carrying amount may not be recoverable. We conduct our long-lived asset impairment analyses in accordance with ASC 360-10-15, "Impairment or Disposal of Long-Lived Assets." ASC 360-10-15 requires us to group assets and liabilities at the lowest level for which identifiable cash flows are largely independent of the cash flows of other assets and liabilities and evaluate the asset group against the sum of the undiscounted future cash flows. If the undiscounted cash flows do not indicate the carrying amount of the asset is recoverable, an impairment charge is measured as the amount by which the carrying amount of the asset group exceeds its fair value based on discounted cash flow analysis or appraisals.

Income Taxes

Income taxes are accounted for under the liability method. Deferred tax assets and liabilities are recognized for the differences between the carrying values of assets and liabilities and their respective income tax bases and for operating losses and tax credit carry forwards. A valuation allowance is provided for the portion of deferred tax assets that is more likely than not to be unrealized. Deferred tax assets and liabilities are measured using the enacted tax rates and laws.

Government Grants

We account for government grants by recognizing the benefit of the grant as qualifying expenditures are incurred provided that there is reasonable assurance that we have complied with all conditions under the terms of the grant and that the amount requested for reimbursement will be received. The government grant reduces the research and development, or R&D, expenses to which it relates on our statement of profit and loss.

Research and Development Costs

Research and development costs are expensed as incurred, net of related refundable investment tax credits, with the exception of non-refundable advance payments for goods or services to be used in future research and development, which are capitalized in accordance with ASC 730, "Research and Development" and included within Prepaid Expenses or Other Assets depending on when the assets will be utilized.

Clinical trial expenses are a component of research and development costs. These expenses include fees paid to contract research organizations and investigators and other service providers, which conduct certain product development activities on our behalf. We use an accrual basis of accounting, based upon estimates of the amount of service completed. In the event payments differ from the amount of service completed, prepaid expense or accrued liabilities amounts are adjusted on the balance sheet. These expenses are based on estimates of the work performed under service agreements, milestones achieved, patient enrollment and experience with similar contracts. We monitor each of these factors to the extent possible and adjust estimates accordingly.

Stock-Based Compensation

Under the fair value recognition provisions of the ASC 718, "Stock Compensation", we use the modified prospective method with respect to options granted to employees and directors. The expense is amortized on a straight-line basis over the graded vesting period.

Restricted Stock Unit Awards

We grant restricted stock unit awards that generally vest and are expensed over afour-year period. We also granted restricted stock unit awards that vest in conjunction with certain performance conditions to certain executive officers and key employees. At each reporting date, we evaluate whether achievement of the performance conditions is probable. Compensation expense is recorded over the appropriate service period based upon our assessment of accomplishing each performance provision or the occurrence of other events that may have caused the awards to accelerate and vest.

Segment Information

We follow the requirements of ASC 280, "Segment Reporting." We haveone operating segment, dedicated to the development and commercialization of cytisinicline for nicotine addiction, with operations located in Canada, the United States and the United Kingdom.

Comprehensive Income (Loss)

Comprehensive income (loss) is comprised of net income (loss) and other comprehensive income (loss). Other comprehensive income (loss) consists of unrealized gains and losses on our available-for-sale marketable securities. We report the components of comprehensive loss in the statement of stockholders' equity.

Loss per Common Share

Basic loss per common share is computed using the weighted average number of common shares outstanding during the period. Diluted loss per common share is computed in accordance with the treasury stock method. The effect of potentially issuable common shares from outstanding stock options, restricted stock unit awards and warrants are anti-dilutive for all periods presented.

Warrants

We account for warrants pursuant to the authoritative guidance on accounting for derivative financial instruments indexed to, and potentially settled in, a company's own stock, on the understanding that in compliance with applicable securities laws, the warrants require the issuance of registered securities upon exercise and therefore do not sufficiently preclude an implied right to net cash settlement. We have warrants classified as equity and these are not reassessed for their fair value at the end of each reporting period. Warrants classified as equity are initially measured at their fair value and recognized as part of stockholders' equity. Determining the

appropriate fair-value model and calculating the fair value of registered warrants requires considerable judgment, including estimating stock price volatility and expected warrant life. The computation of expected volatility was based on the historical volatility of comparable companies from a representative peer group selected based on industry and market capitalization. A small change in the estimates used may have a relatively large change in the estimated valuation. We use the Black-Scholes pricing model to value the warrants.

Reporting Currency and Foreign Currency Translation

Our functional and reporting currency is the U.S. dollar. Revenues and expenses denominated in other than U.S. dollars are translated at average monthly rates.

The functional currency of our foreign subsidiary is the U.S. dollar. For this foreign operation, assets and liabilities denominated in other than U.S. dollars are translated at the period-end rates for monetary assets and liabilities and historical rates for non-monetary assets and liabilities. Revenues and expenses denominated in other than U.S. dollars are translated at average monthly rates. Gains and losses from this translation are recognized in the consolidated statement of loss.

Recently Adopted Accounting Policies

In February 2016, the FASB established Topic 842, Leases, by issuing Accounting Standards Update ASU No. 2016-02, which requires lessees to recognize leases on-balance sheet and disclose key information about leasing arrangements. The new standard establishes a right-of-use, or ROU, model that requires a lessee to recognize a ROU asset and lease liability on the balance sheet for all leases with a term longer than 12 months. Leases were classified as finance or operating, with classification affecting the pattern and classification of expense recognition in the consolidated statements of loss and comprehensive loss.

We adopted the standard on the effective date of January 1, 2019 and elected to use the modified retrospective method. Consequently, financial information will not be updated and the disclosures required under the new standard will not be provided for dates and periods before January 1, 2019. We elected the short-term lease recognition exemption for all leases that qualify. This means, for those leases that qualify, we will not recognize ROU assets or lease liabilities, and this includes not recognizing ROU assets or lease liabilities for existing short-term leases of those assets in transition. We also elected the available practical expedients and implemented internal controls to enable the preparation of financial information on adoption.

The standard had a material impact on our consolidated balance sheets, but did not have an impact on our consolidated statements of loss and comprehensive loss. The most significant impact was the recognition of ROU assets, of $0.5 million, and lease liabilities, of $0.5 million, for operating leases, while our accounting for finance leases remained substantially unchanged.

In August 2018, the FASB issued Accounting Standards Update 2018-13, Fair Value Measurement, which both modifies and clarifies the disclosure requirements for fair value measurement. This update is effective for financial statements issued for fiscal years beginning after December 15, 2019, with early adoption permitted. The adoption of this standard did not have a significant impact on our financial position or results of operations.

In August 2020, the FASB issued Accounting Standards Update No. 2020-06, Debt – Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging – Contracts in Entity's Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity's Own Equity, or ASU 2020-06. ASU 2020-06 simplifies the accounting for convertible instruments, the accounting for contracts in an entity's own equity, and the related earnings per share calculations. The new standard is effective for fiscal years beginning after December 15, 2021 and early adoption is permitted as of the beginning of an interim period for which financial statements (interim or annual) have not been issued or have not been made available for issuance.

We elected to early adopt the standard effective in 2021. The adoption of this standard did not have any impact on our prior period financial statements.

As a result of adopting ASU 2020-06, we are not required to separately record the conversion feature of the convertible debt but instead account for the convertible instrument and conversion feature as a single unit of debt.

3. FINANCIAL INSTRUMENTS AND RISK

For certain of our financial instruments, including cash and cash equivalents, accounts payable, accrued liabilities other, accrued clinical liabilities and accrued compensation carrying values approximate fair value due to their short-term nature. Our cash equivalents are recorded at fair value.

Financial risk is the risk to our results of operations that arises from fluctuations in interest rates and foreign exchange rates and the degree of volatility of these rates as well as credit risk associated with the financial stability of the issuers of the financial instruments. Foreign exchange rate risk arises as a portion of our investments which finance operations and a portion of our expenses are denominated in other than U.S. dollars.

We invest our excess cash in accordance with investment guidelines, which limit our credit exposure to any one financial institution or corporation other than securities issued by the U.S. government. We only invest in A (or equivalent) rated securities with maturities of one year or less. These securities generally mature within one year or less and in some cases are not collateralized. At December 31, 2021 the average days to maturity of our portfolio of cash equivalents and marketable securities was zero days. We do not use derivative instruments to hedge against any of these financial risks.

4. GOVERNMENT GRANT

In July 2021, we were awarded a grant from the National Institute on Drug Abuse, or NIDA, of the National Institutes of Health, or NIH, to evaluate the use of cytisinicline as a treatment for cessation of nicotine e-cigarette use. This initial grant award, in the amount of $0.3 million, commenced on August 1, 2021, and is being utilized to complete critical regulatory and clinical operational activities, such as protocol finalization, clinical trial site identification, drug packaging, and submission of a new Investigational New Drug Application, or IND, to the U.S. Food and Drug Administration, or FDA, for investigating cytisinicline in nicotine e-cigarette users.

For the year ended December 31, 2021 we incurred $0.3 million in qualifying R&D expenditures under the NIH grant which has been recorded as a reduction in R&D expense. As of December 31, 2021 we had $0.2 million in grant receivable related to the NIH grant.

5. INTANGIBLES

All of our intangible assets are subject to amortization and are amortized using the straight-line method over their estimated useful life.

We acquired license and supply agreements, in relation to cytisinicline, upon the acquisition of Extab Corporation, or Extab, in 2015. The agreements were determined to have a fair value of $3.1 million with an estimated useful life of 14 years.

The components of intangible assets were as follows:

	December 31, 2021			December 31, 2020		
	Gross Carrying Value	Accumulated Amortization	Net Carrying Value	Gross Carrying Value	Accumulated Amortization	Net Carrying Value
License Agreements	$ 3,117	$ (1,476)	$ 1,641	$ 3,117	$ (1,253)	$ 1,864

For the year ended December 31, 2021 and 2020 we recorded license agreement amortization expense of $0.2 million and $0.2 million, respectively. The following table outlines the estimated future amortization expense related to intangible assets held as of December 31, 2021:

Year Ending December 31,	
2022	223
2023	223
2024	223
2025	223
Thereafter	749
Total	**$ 1,641**

We evaluate the carrying amount of intangible assets periodically by taking into account events or circumstances that may warrant revised estimates of useful life or that indicate the asset may be impaired. We conducted an impairment analysis for long lived assets, including the license and supply agreements for the active pharmaceutical ingredient cytisinicline, and concluded that there were no indicators of impairment identified as of December 31, 2021.

6. LICENSE AGREEMENTS

Sopharma License and Supply Agreements

In 2009 and 2010, we entered into a license agreement, or the Sopharma License Agreement, and a supply agreement, or the Sopharma Supply Agreement, with Sopharma, AD, or Sopharma. Pursuant to the Sopharma License Agreement, we were granted access to all available manufacturing, efficacy and safety data related to cytisinicline, as well as a granted patent in several European countries including Germany, France and Italy related to new oral dosage forms of cytisinicline providing enhanced stability. Additional rights granted under the Sopharma License Agreement include the exclusive use of, and the right to sublicense, the trademark Tabex in all territories—other than certain countries in Central and Eastern Europe, Scandinavia, North Africa, the Middle East and Central Asia, as well as Vietnam, where Sopharma or its affiliates and agents already market Tabex—in connection with the marketing, distribution and sale of products. Under the Sopharma License Agreement, we agreed to pay a nonrefundable license fee. In addition, we agreed to make certain royalty payments equal to a mid-teens percentage of all net sales of Tabex branded products in our territory during the term of the Sopharma License Agreement, including those sold by a third party pursuant to any sublicense which may be granted by us. We have agreed to cooperate with Sopharma in the defense against any actual or threatened infringement claims with respect to Tabex. Sopharma has the right to terminate the Sopharma License Agreement upon the termination or expiration of the Sopharma Supply Agreement. The Sopharma License Agreement will also terminate under customary termination provisions including bankruptcy or insolvency and material breach. To date, any amounts paid to Sopharma pursuant to the Sopharma License Agreement have been immaterial.

A cross-license exists between us and Sopharma whereby we grant to Sopharma rights to any patents or patent applications or other intellectual property rights filed by us in Sopharma territories.

On May 14, 2015, we and Sopharma entered into an amendment to the Sopharma License Agreement. Among other things, the amendment to the Sopharma License Agreement reduced the royalty payments payable by us to Sopharma from a percentage in the mid-teens to a percentage in the mid-single digits and extended the term of the Sopharma License Agreement until May 26, 2029.

On July 28, 2017, we and Sopharma entered into the amended and restated Sopharma Supply Agreement. Pursuant to the amended and restated Sopharma Supply Agreement, for territories as detailed in the licensing agreement, we will exclusively purchase all of our cytisinicline from Sopharma, and Sopharma agrees to exclusively supply all such cytisinicline requested by us, and we extended the term to 2037. In addition, we will have full access to the cytisinicline supply chain and Sopharma will manufacture sufficient cytisinicline to meet a forecast for a specified demand of cytisinicline for the five years commencing shortly after the commencement of the agreement, with the forecast to be updated regularly thereafter. Each of us and Sopharma may terminate the Sopharma Supply Agreement in the event of the other party's material breach or bankruptcy or insolvency.

University of Bristol License Agreement

In July 2016, we entered into a license agreement with the University of Bristol, or the University of Bristol License Agreement. Under the University of Bristol License Agreement, we received exclusive and nonexclusive licenses from the University of Bristol to certain patent and technology rights resulting from research activities into cytisinicline and its derivatives for use in smoking cessation, including a number of patent applications related to novel approaches to cytisinicline binding at the nicotinic receptor level. Any patents issued in connection with these applications would be scheduled to expire on February 5, 2036 at the earliest.

In consideration of rights granted by the University of Bristol, we agreed to pay amounts of up to $3.2 million, in the aggregate, tied to a financing milestone and to specific clinical development and commercialization milestones resulting from activities covered by the University of Bristol License Agreement. Additionally, if we successfully commercialize product candidates subject to the University of Bristol License Agreement, we are responsible for royalty payments in the low-single digits and payments up to a percentage in the mid-teens of any sublicense income, subject to specified exceptions, based upon net sales of such licensed products.

On January 22, 2018, we and the University of Bristol entered into an amendment to the University of Bristol License Agreement. Pursuant to the amended University of Bristol License Agreement, we received exclusive rights for all human medicinal uses of cytisinicline across all therapeutic categories from the University of Bristol from research activities into cytisinicline and its derivatives. In consideration of rights granted by the amended University of Bristol License Agreement, we agreed to pay an initial amount of $37,500 upon the execution of the amended University of Bristol License Agreement, and additional amounts of up to $1.7 million, in the aggregate, tied to a financing milestone and to specific clinical development and commercialization milestones resulting from activities covered by the amended University of Bristol License Agreement, in addition to amounts under the original University of Bristol License Agreement of up to $3.2 million in the aggregate, tied to specific financing, development and commercialization milestones. Additionally, if we successfully commercialize any product candidate subject to the amended University of Bristol License Agreement or to the original University of Bristol License Agreement, we will be responsible, as provided in the original University of Bristol License Agreement, for royalty payments in the low-single digits and payments up to a

percentage in the mid-teens of any sublicense income, subject to specified exceptions, based upon net sales of such licensed products. Up to December 31, 2021, we had paid the University of Bristol $125,000 pursuant to the University of Bristol License Agreement.

Unless otherwise terminated, the University of Bristol License Agreement will continue until the earlier of July 2036 or the expiration of the last patent claim subject to the University of Bristol License Agreement. We may terminate the University of Bristol License Agreement for convenience upon a specified number of days' prior notice to the University of Bristol. The University of Bristol License Agreement will terminate under customary termination provisions including bankruptcy or insolvency or its material breach of the agreement. Under the terms of the University of Bristol License Agreement, we had provided 100 grams of cytisinicline to the University of Bristol as an initial contribution.

7. FAIR VALUE MEASUREMENTS

Assets and liabilities recorded at fair value in the balance sheets are categorized based upon the level of judgment associated with the inputs used to measure their fair value. For certain of our financial instruments including amounts receivable and accounts payable the carrying values approximate fair value due to their short-term nature.

ASC 820 "Fair Value Measurements and Disclosures," specifies a hierarchy of valuation techniques based on whether the inputs to those valuation techniques are observable or unobservable. In accordance with ASC 820, these inputs are summarized in the three broad level listed below:

- Level 1 – Quoted prices in active markets for identical securities.
- Level 2 – Other significant inputs that are observable through corroboration with market data (including quoted prices in active markets for similar securities).
- Level 3 – Significant unobservable inputs that reflect management's best estimate of what market participants would use in pricing the asset or liability.

As quoted prices in active markets are not readily available for certain financial instruments, we obtain estimates for the fair value of financial instruments through third-party pricing service providers.

In determining the appropriate levels, we performed a detailed analysis of the assets and liabilities that are subject to ASC 820.

We invest our excess cash in accordance with investment guidelines that limit the credit exposure to any one financial institution other than securities issued by the U.S. Government. These securities are not collateralized and mature within one year.

A description of the valuation techniques applied to our financial instruments measured at fair value on a recurring basis follows.

Financial Instruments

Cash and cash equivalents

Significant amounts of cash are held on deposit with large well-established U.S. and Canadian financial institutions.

U.S. Government and Agency Securities

U.S. Government Securities U.S. government securities are valued using quoted market prices. Valuation adjustments are not applied. Accordingly, U.S. government securities are categorized in Level 1 of the fair value hierarchy.

U.S. Agency Securities U.S. agency securities are comprised of two main categories consisting of callable and non-callable agency issued debt securities. Non-callable agency issued debt securities are generally valued using quoted market prices. Callable agency issued debt securities are valued by benchmarking model-derived prices to quoted market prices and trade data for identical or comparable securities. Actively traded non-callable agency issued debt securities are categorized in Level 1 of the fair value hierarchy.

The following table presents information about our assets and liabilities that are measured at fair value on a recurring basis, and indicates the fair value hierarchy of the valuation techniques we utilized to determine such fair value (in thousands):

December 31, 2021	Level 1	Level 2	Level 3	Total
Assets				
Money market securities (cash equivalents)	41,859	—	—	41,859
Restricted cash *(Note 11)*	50	—	—	50
Total assets	**$ 41,909**	**$ —**	**$ —**	**$ 41,909**

December 31, 2020	Level 1	Level 2	Level 3	Total
Assets				
Money market securities (cash equivalents)	35,380	—	—	35,380
Restricted cash *(Note 11)*	50	—	—	50
Total assets	**$ 35,430**	**$ —**	**$ —**	**$ 35,430**

Cash and cash equivalents (in thousands):

December 31, 2021	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Money market securities	41,859	—	—	41,859
Total cash and cash equivalents	**$ 41,859**	**$ —**	**$ —**	**$ 41,859**
Money market securities (restricted cash)	50	—	—	50
Total restricted cash	**$ 50**	**$ —**	**$ —**	**$ 50**

December 31, 2020	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Money market securities	35,380	—	—	35,380
Total cash and cash equivalents	**$ 35,380**	**$ —**	**$ —**	**$ 35,380**
Money market securities (restricted cash)	50	—	—	50
Total restricted cash	**$ 50**	**$ —**	**$ —**	**$ 50**

We only invest in A (or equivalent) rated securities with maturities of one year or less.

Fair Value of Long-Term Debt

December 2021 Convertible Debt

The principal amount, carrying value and related estimated fair value of our convertible debt reported in the consolidated balance sheets as of December 31, 2021 and December 31, 2020 was as follows (in thousands). The aggregate fair value of the principal amount of the convertible debt is a Level 2 fair value measurement.

	December 31, 2021			December 31, 2020		
	Principal Amount	Carrying Value	Fair Value	Principal Amount	Carrying Value	Fair Value
December 2021 Convertible Debt	$ 15,000	$ 14,920	$ 15,204	$ —	$ —	$ —

8. PROPERTY AND EQUIPMENT

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

	Cost	Accumulated Depreciation	Net Book Value
December 31, 2021			
Computer equipment	$ 141	$ 138	$ 3
Furniture and fixtures	42	42	—
Leasehold improvements	26	19	7
Computer software	74	74	—
Equipment under capital lease	19	14	5
Total property and equipment	$ 302	$ 287	$ 15

9. OTHER ASSETS

Other assets include deferred share issues costs and deposits paid for office space in accordance with the terms of the operating lease agreements.

10. CONVERTIBLE DEBT

On December 22, 2021, the Company entered into a $25.0 million contingent convertible debt agreement, or Debt Agreement, with Silicon Valley Bank, or SVB, and SVB Innovation Credit Fund VIII, L.P., or, together with SVB, the Lenders. As part of the contingent convertible debt agreement, the Lenders funded $15.0 million in the form of convertible indebtedness, or Convertible Debt, at closing. Subject to certain terms and conditions, we may borrow additional non-convertible term loans in an aggregate original principal amount of up to $10.0 million.

Under the terms of the agreement, the Convertible Debt matures December 22, 2023 and may be extended to December 22, 2024 upon our written request and SVB's approval on or prior to December 22, 2023. The Convertible Debt will accrue interest at the aggregate of (a) a floating rate per annum equal to the greater of (i) 2.25% and (ii) the prime rate minus 1.0%, which interest is payable in cash monthly in arrears, and (b) 7.0% per annum, which interest shall compound monthly.

Subject to certain terms and conditions, the Lenders may convert all or any part of the outstanding Convertible Debt and accrued and unpaid interest at any time prior to maturity into shares of our common stock at a conversion price equal to Subject to certain terms and conditions, the Lenders may convert all or any part of the outstanding Convertible Debt and accrued and unpaid interest at any time prior to maturity into shares of our common stock at a conversion price equal to $9.34 per share, subject to customary anti-dilution adjustments. Additionally, all outstanding Convertible Debt, including accrued and unpaid interest, will mandatorily convert into shares of our common stock, at the conversion price, on such date, if any, when the closing price per share of our common stock has been equal to or greater than $24.00 for thirty consecutive trading days prior to such date.

We have the right, or Call Right, at any time to repay and retire all (but not less than all) of the outstanding Convertible Debt and accrued and unpaid interest, if any, prior to its conversion by payment of a premium determined based on the date of such repayment equal to:

i. 125% of the principal amount of the Convertible Debt including accrued paid-in-kind interest, or PIK, if the Call Right is exercised on or before the 18-month anniversary of the date of the Debt Agreement; and
ii. 150% of the principal amount of the Convertible Debt including accrued PIK, if the Call Right is exercised after the 18-month anniversary of the date of the Debt Agreement,

in either case together with all accrued and unpaid interest on the principal balance of the Convertible Debt. If the Call Right is exercised by us, the Lenders will retain certain lookback rights in the event we enter into an agreement to be acquired in the 12 months following the exercise of the Call Right. We agreed to grant the Lenders a security interest in virtually all of our assets, including our patents and other intellectual property as security for our obligations under the Debt Agreement.

Under ASU 2020-06, the embedded conversion feature was not required to be bifurcated and recognized separately, as a result the convertible debt including the conversion feature has been recognized as a single unit of debt. The debt issuance costs have been recognized against the single unit of debt and will be amortized into interest expense over the term of the loan.

As of December 31, 2021, the Convertible Debt balance was comprised of the following:

	Year Ended December 31, 2021
Convertible Debt Information	
Principal	$ 15,000
Transaction Costs	$ (109)
Accrued paid-in-kind interest	29
	14,920

11. INCOME TAX

[a] We are a Delaware incorporated company subject to blended US Federal and state statutory rates for December 31, 2021, 2020 and 2019 of21%. For the purposes of estimating the tax rate in effect at the time that deferred tax assets and liabilities are expected to reverse, management uses the furthest out available future tax rate in the applicable jurisdictions.

U.S. and foreign components of income (loss) before income taxes were as follows (in thousands):

(In thousands)	2021	2020	2019
U.S.	$ (31,411)	$ (12,304)	$ (10,028)
Foreign	(1,741)	(2,426)	(6,367)
Income (loss) before income taxes	$ (33,152)	$ (14,730)	$ (16,395)

Income tax expense/(recovery) consisted of the following (in thousands):

(In thousands)	2021	2020	2019
Income tax recovery at statutory rates (at a rate of21% for all years presented)	$ (6,962)	$ (3,094)	$ (3,490)
Expenses not deducted for tax purposes	224	118	116
Effect of tax rate changes on deferred tax assets and liabilities	17	34	(13)
Rate differential on foreign earnings	(77)	(103)	(296)
Investment tax credits	(134)	(23)	(84)
Change in valuation allowance	7,544	3,662	(3,246)
Reassessment of previously recognized net operating losses	(620)	—	7,192
Reversal of previously accrued taxes due to IRS reassessment	—	—	(221)
Other	8	(594)	(179)
Income tax expense/(recovery)	$ —	$ —	$ (221)

[b] The tax effects of the temporary differences and carryforwards that give rise to deferred tax assets and liabilities are as follows (in thousands):

	2021	2020
Deferred tax assets		
Tax basis in excess of book value of assets	$ 897	$ 892
Non-capital loss carryforwards	39,356	35,596
Research and development deductions and credits	7,058	7,010
§59(e) Capitalized R&D expenses	7,159	3,757
Other	1,018	813
Total deferred tax assets	55,488	48,068
Valuation allowance	(55,082)	(47,539)
Net deferred assets	406	529
Deferred tax liabilities		
Other	(406)	(529)
Total deferred tax liabilities	(406)	(529)
Net deferred tax assets	—	—

A valuation allowance is recorded when it is more likely than not that all or some portion of the deferred tax assets, or DTAs, will not be realized. Management assesses the need for a valuation allowance against the deferred tax assets when considering both positive and negative evidence related to whether it is more likely than not that the deferred tax assets will be realized. In evaluating the ability to recover the deferred tax assets within the jurisdiction from which they arise, all available positive and negative evidence is considered, including scheduled reversals of deferred tax liabilities, projected future growth, tax-planning strategies, and results of recent operations.

Due to the uncertainty surrounding the realization of deductible tax attributes in future tax returns, the Company has recorded a valuation allowance for deferred tax assets of $55.5 million to reduce the DTAs to zero as of December 31, 2021. The valuation allowance increased by approximately $7.5 million during the year ended December 31, 2021. The amount of the DTA considered realizable, however, could be adjusted if estimates of future taxable income during the carryforward period increased or if objective negative evidence in the form of cumulative losses is no longer present and additional weight is given to subjective evidence such as our projections for growth.

The Company has total net operating loss carryforwards for federal tax purposes of approximately $47.4 million ($34.8 million—2020) as of December 31, 2021, most of which begin to expire in 2021. Approximately $37.3 million of the federal net operating losses will carryforward indefinitely. Federal net operating losses generated after January 1, 2018 were originally available to offset 80% of taxable income for any given future tax year and will be carried forward indefinitely. However, with the passage of the 2020 CARES Act, the 80% limitation is temporarily removed for tax years 2018 to 2020. The company has research and development tax credit carryforwards of approximately $0.4 million ($0.3 million—2020) as of December 31, 2021, which expire in2041. The operating loss carryforwards and research and development tax credits may be limited due to a change in control in the Company's ownership as defined by the Internal Revenue Code Section 382. Any future changes in the Company's ownership may limit the use of such carryforward benefits.

The Company’s effective income tax rate for the periods presented differ from the statutory rate of21% primarily due to current year net losses and the full valuation allowance on the U.S. deferred tax assets. The company files income tax returns in the U.S., Canada, and U.K. At December 31, 2021, the company has Canadian non-capital loss carryforwards of $109.5 million ($105.6 million—2020) and research tax credits of $2.7 million ($2.8 million—2020), both of which will expire in2041. In addition, the Company has unclaimed tax deductions of approximately $16 million related to scientific research and experimental development expenditures available to carry forward indefinitely to reduce Canadian taxable income of future years. The UK net operating loss carryforwards of $3.5 million (2020—$3.2 million) will carryforward indefinitely.

[c] A reconciliation of the unrecognized tax benefits of uncertain tax positions for the year ended December 31, 2021 is as follows (in thousands):

	Year ended December 31,		
	2021	2020	2019
Balance at January 1	$ 767	$ 724	$ 717
Gross increases (decreases) related to prior period tax positions	(6)	43	7
Gross increases (decreases) related to current period tax positions	—	—	—
Decreases relating to settlements with tax authorities	—	—	—
Reductions due to lapses of statute of limitations	—	—	—
Balance at December 31	$ 761	$ 767	$ 724

As of December 31, 2021, unrecognized benefits of approximately $0.8 million, if recognized, would affect our effective tax rate, and would reduce our deferred tax assets.

Our accounting policy is to treat interest and penalties relating to unrecognized tax benefits as a component of income taxes. As of December 31, 2021 and December 31, 2020 we had no accrued interest and penalties related to income taxes.

We are subject to taxes in Canada, the U.K. and the U.S. until the applicable statute of limitations expires. Tax audits by their very nature are often complex and can require several years to complete.

Tax Jurisdiction	Years open to examination
Canada	2017 to 2021
United Kingdom	2013 to 2021
US	2018 to 2021

12. COMMON STOCK

[a] Authorized

150,000,000 authorized common voting shares, par value of $0.001, and 5,000,000 preferred shares, par value of $0.001.

[b] Issued and outstanding shares

Purchase Agreement and Financing with Lincoln Park Capital

On September 14, 2017 we and Lincoln Park Capital Fund, LLC, or LPC, entered into a share and unit purchase agreement, which was amended on March 12, 2020, or the Purchase Agreement, pursuant to which we have the right to sell to LPC up to $11.0 million in shares of our common stock, par value $0.001 per share, subject to certain limitations and conditions set forth in the Purchase Agreement. On May 22, 2018 we obtained the requisite stockholder authorization to sell shares of our common stock to LPC in excess of 20% of our outstanding shares of common stock (as of the date we entered into the Purchase Agreement) in order to be able to sell to LPC the full amount remaining under the Purchase Agreement.

Pursuant to the Purchase Agreement, LPC initially purchased 1,644 of our units, or the Units, at a purchase price of $608 per unit, with each Unit consisting of (a) one share of our common stock and (b) one warrant to purchase one-quarter of a share of common stock at an exercise price of $699.20 per share, or Warrant. Each Warrant became exercisable six months following the issuance date until the date that is five years and six months after the issuance date and is subject to customary adjustments. The Warrants were issued only as part of the Units in the initial purchase of $1.0 million and no warrants shall be issued in connection with any other purchases of common stock under the Purchase Agreement.

After the initial purchase, if our stock price is above $1.00, as often as every other business day over the 54-month term of the Purchase Agreement, and up to an aggregate amount of an additional $10.0 million (subject to certain limitations) of shares of common stock, we have the right, from time to time, in our sole discretion and subject to certain conditions to direct LPC to purchase up to 7,500 shares of common stock. The purchase price of shares of common stock pursuant to the Purchase Agreement will be based on prevailing market prices of common stock at the time of sales without any fixed discount, and we will control the timing and

amount of any sales of common stock to LPC. As consideration for entering into the Purchase Agreement, we issued to LPC 617 shares of common stock in September 2017 and, in connection with the amendment of the Purchase Agreement in March 2020, we agreed to pay to LPC $0.1 million as an expense reimbursement. The consideration of 617 shares of our common stock were fair valued based on the closing price of our common stock as at the transaction date and recognized as part of offering expenses.

During the year ended December 31, 2021, we offered and sold zero shares of our common stock pursuant to the Purchase Agreement with LPC. Since entering into the Purchase Agreement, from September 14, 2017 through December 31, 2020, we offered and sold an aggregate of 27,868 shares of our common stock, including the 1,644 shares that were part of the initial purchase of Units. These aggregate sales resulted in gross proceeds to us of approximately $4.4 million and offering expenses of $0.5 million. The purchase agreement will expire on March 14, 2022.

December 2019 Public Offering

On December 17, 2019, we completed an underwritten registered public offering, pursuant to which we sold 478,875 Class A Units at a price per unit of $12.00 and 6,256 Class B Units at a price per unit of $999.60.

Each Class A Unit consisted of one share of our common stock and a warrant to purchase one share of common stock.

Each Class B Unit consisted of one share of Series B Convertible Preferred Stock, par value $0.001 per share, convertible at any time at the holder's option into 83 shares of common stock, and warrants to purchase 83 shares of common stock.

Each warrant was immediately exercisable, expires on the five year anniversary of the date of issuance and is exercisable at a price per share of common stock of $6.60, subject to adjustment in the event of subsequent equity sales of common stock or securities convertible into common stock for an exercise price per share less than the exercise price per share of the warrants then in effect, provided, however, that the exercise price of the warrants cannot be reduced to an amount less than $1.2 per share of common stock. Additionally, subject to certain exceptions, if, after December 17, 2019, (i) the volume weighted average price of the common stock for each of 30 consecutive trading days, or the 2019 Measurement Period, which 2019 Measurement Period commences on the closing date, exceeds 300% of the exercise price (subject to adjustments for stock splits, recapitalizations, stock dividends and similar transactions), (ii) the average daily trading volume for such 2019 Measurement Period exceeds $500,000 per trading day and (iii) certain other equity conditions are met, and subject to a beneficial ownership limitation, then we may call for cancellation of all or any portion of the warrants then outstanding.

The Class A Units and Class B Units were not certificated and the shares of common stock, Series B Convertible Preferred Stock and warrants comprising such units were immediately separable and were issued separately in the public offering. The Class A Units and B Units were offered by us pursuant to the registration statement on Form S-1 (File No. 333-234530), and each amendment thereto, which was initially filed with the SEC on November 6, 2019 and declared effective by the SEC on December 17, 2019.

In addition, pursuant to the Underwriting Agreement we entered into with Ladenburg Thalmann & Co. Inc., or Ladenburg, on December 17, 2019, we granted Ladenburg a 45 day option, or the 2019 Overallotment Option, to purchase up to 150,000 additional shares of common stock and/or warrants to purchase up to 150,000 shares of common stock solely to cover over-allotments. The 2019 Overallotment Option was exercised in full on December 17, 2019.

The public offering raised total gross proceeds of $13.8 million and after deducting $1.5 million in underwriting discounts and commissions and offering expenses, we received net proceeds of $12.3 million.

The underwriting discounts and commissions and offering expenses have been charged against the gross proceeds.

As of December 31, 2021, all 6,256 shares of the Series B Convertible Preferred Stock had been converted into 521,124 shares of common stock, and no shares of the Series B Convertible Preferred Stock remained outstanding.

April 2020 Private Placement

On April 27, 2020 and April 28, 2020, we entered into subscription agreements with certain accredited investors pursuant to which we sold to the purchasers in a private placement approximately 280,782 units, or Units, each consisting of (i) one share of common stock, and (ii) a warrant to purchase 0.75 shares of common stock at an offering price of $6.60 per Unit, for aggregate gross proceeds of approximately $1.9 million. The placement agent received a cash commission on the gross proceeds from the sale of the Units and was issued a five (5) year warrant upon substantially similar terms as the investor warrants to purchase 25,270 shares of common stock at an initial exercise price of $7.59 per share. The net proceeds to us, after deducting placement agent expenses and commissions and offering expenses was approximately $1.6 million.

Each warrant became exercisable on October 27, 2020, the six-month anniversary of the initial closing date of the offering, through April 27, 2025, which is the five-year anniversary of the initial closing date of the offering. The warrants issued pursuant to subscription agreements executed on April 27, 2020 are exercisable at a price per share of common stock of $7.24, subject to adjustment, and the warrants issued pursuant to subscription agreements executed on April 28, 2020 are exercisable at a price per share of common stock of $7.32, subject to adjustment. Additionally, subject to certain exceptions, if, after the initial exercise date, (i) the volume weighted average price of the common stock for each of 30 consecutive trading days, or the Measurement Period, which, Measurement Period commences on the closing date, exceeds 300% of the exercise price (subject to adjustments for stock splits, recapitalizations, stock dividends and similar transactions), (ii) the average daily trading volume for such Measurement Period exceeds $500,000 per trading day and (iii) certain other equity conditions are met, and subject to a beneficial ownership limitation, then we may call for cancellation of all or any portion of the warrants then outstanding.

Placement agent expenses and commissions and offering expenses have been charged against the gross proceeds.

July 2020 Registered Direct Offering

On July 1, 2020, we completed a registered direct offering, pursuant to which we sold 731,707 shares of our common stock at a price of $8.20 per share.

The registered direct offering raised total gross proceeds of approximately $6.0 million, and after deducting approximately $0.7 million in placement agent fees and offering expenses, we received net proceeds of approximately $5.3 million.

The placement agent fees and offering expenses have been charged against the gross proceeds.

August 2020 Public Offering

On August 6, 2020, we completed an underwritten public offering of our securities, pursuant to which we sold an aggregate of (a) 569,043 shares of our common stock, including 92,856 shares subject to the underwriter's option to purchase additional shares, or the August Shares, and (b) pre-funded warrants to purchase 142,857 shares of our common stock, or the Pre-Funded Warrants, to the underwriter. The August Shares were sold at the public offering price of $10.50 per share. The Pre-Funded Warrants were sold at a public offering price of $10.499, which represents the per share public offering price for the August Shares less a $0.001 per share exercise price for each such Pre-Funded Warrant.

The Pre-Funded Warrants are exercisable at any time after the date of issuance. A holder of Pre-Funded Warrants may not exercise the warrant if the holder, together with its affiliates, would beneficially own more than 9.99% of the number of shares of common stock outstanding immediately after giving effect to such exercise. A holder of Pre-Funded Warrants may increase or decrease this percentage, but not in excess of 19.99%, by providing at least 61 days' prior notice to us.

The underwritten public offering raised total gross proceeds of approximately $7.5 million and after deducting approximately $0.7 million in underwriting discounts and commissions and offering expenses, we received net proceeds of approximately $6.8 million. The underwriting discounts and commissions and offering expenses have been charged against the gross proceeds.

December 2020 Public Offering

On December 7, 2020, we completed an underwritten public offering of our securities, pursuant to which we sold an aggregate of 2,472,500 shares of our common stock, including 322,500 shares subject to the underwriter's option to purchase additional shares, or the December Shares. The December Shares were sold at the public offering price of $7.00 per share.

We also issued a warrant to purchase 50,000 shares of common stock to the representative of the underwriters, the Representative's Warrant, as a portion of the underwriting compensation payable in connection with this offering. The Representative's Warrant became exercisable beginning on May 31, 2021, with an exercise price of $8.75 per share and a term of five years. Under ASC 260, the fair value of the Representative's Warrant of $0.3 million was charged against Additional Paid-In Capital.

The underwritten public offering raised total gross proceeds of approximately $17.3 million and after deducting approximately $1.5 million in underwriting discounts and commissions and offering expenses, we received net proceeds of approximately $15.8 million. The underwriting discounts and commissions and offering expenses have been charged against the gross proceeds.

May 2021 Public Offering

On May 27, 2021, we completed an underwritten public offering of our securities, pursuant to which we sold an aggregate of 8,285,714 shares of our common stock, including 428,571 shares subject to the underwriter's option to purchase additional shares, or the May Shares. The May Shares were sold at the public offering price of $3.00 per share.

The underwritten public offering raised total gross proceeds of approximately $23.0 million and after deducting approximately $1.7 million in underwriting discounts and commissions and offering expenses, we received net proceeds of approximately $21.3 million. The underwriting discounts and commissions and offering expenses have been charged against the gross proceeds.

At-the-Market Sales Agreement

On December 21, 2022, we entered into an At-the-Market Offering Sales Agreement, or ATM with Virtu Americas, LLC, as sales agent, pursuant to which we may sell shares of common stock with an aggregate offering price of up to $25 million. During the year ended December 31, 2021, we did not sell any shares under the ATM. As of December 31, 2021, we had $25.0 million available in our ATM.

Equity Award Issuances and Settlements

During the year ended December 31, 2021, we did not issue any shares of common stock to satisfy stock option exercises and issued 231 shares of common stock to satisfy restricted stock unit settlements, compared with the issuance of no shares of common to satisfy stock option exercises and 236 shares of common stock to satisfy restricted stock unit settlements for the year ended December 31, 2020.

[c] Stock options

2018 Equity Incentive Plan

As of December 31, 2021, we had reserved, pursuant to the 2018 Equity Incentive Plan, or the 2018 Plan, 521,100 common shares for issuance upon exercise of stock options and settlement of restricted stock units by employees, directors, officers and consultants of ours, of which 463,705 were reserved for options currently outstanding, 53,250 for restricted stock units currently outstanding, and 4,145 were available for future equity grants.

Under the 2018 Plan, we may grant options to purchase common shares or restricted stock units to our employees, directors, officers and consultants. The exercise price of the options is determined by our board of directors but will be at least equal to the fair value of the common shares at the grant date. The options vest in accordance with terms as determined by our board of directors, typically over three to four years for options issued to employees and consultants, and over one to three years for members of our board of directors. The expiry date for each option is set by our board of directors with a maximum expiry date of ten years from the date of grant. In addition, the 2018 Plan allows for accelerated vesting of outstanding equity awards in the event of a change in control. The terms for accelerated vesting, in the event of a change in control, is determined at our discretion and defined under the employment agreements for our officers and certain of our employees.

New Employee Inducement Grants

We grant stock options as a material inducement to new employees for entering into employment agreements with us in accordance with Nasdaq Listing Rule 5635(c)(4). The stock options approved under the inducement grant were issued pursuant to a stock option agreement on terms substantially similar to our 2018 Equity Incentive Plan. The exercise price of the options is determined by our board of directors but will be at least equal to the fair value of the common shares at the grant date. The options vest in accordance with terms as determined by our board of directors. The expiry date for each option is set by our board of directors with a maximum expiry date of ten years from the date of grant. For the year ended December 31, 2021 we granted 45,000 stock options to new employees. As of December 31, 2021, 45,000 stock options granted as new employee inducement grants were outstanding.

2017 Equity Incentive Plan

As of December 31, 2021, we had reserved, pursuant to the 2017 Equity Incentive Plan, or the 2017 Plan, 13,156 common shares for issuance upon exercise of stock options, currently outstanding, by employees, directors and officers of ours. Upon the effectiveness of our 2018 Plan, we ceased granting equity awards under our 2017 Plan.

Under the 2017 Plan, we granted options to purchase common shares or restricted stock units to our employees, directors, officers and consultants. The exercise price of the options was determined by our board of directors but was at least equal to the fair value of the common shares at the grant date. The options vest in accordance with terms as determined by our board of directors, typically over three to four years for options issued to employees and consultants, and over one tothree years for members of our board of directors. The expiry date for each option was set by our board of directors with a maximum expiry date of ten years from the date of grant. In addition, the 2017 Plan allows for accelerated vesting of outstanding equity awards in the event of a change in control. The terms for accelerated vesting, in the event of a change in control, is determined at our discretion and defined under the employment agreements for our officers and certain of our employees.

2010 Performance Incentive Plan

As of December 31, 2021, we had reserved, pursuant to the 2010 Performance Incentive Plan, or the 2010 Plan,229 common shares for issuance upon exercise of stock options, currently outstanding, by employees, directors, officers and consultants of ours.

Under the 2010 Plan we granted options to purchase common shares and restricted stock units to our employees, directors, officers and consultants. The exercise price of the options was determined by our board of directors and was at least equal to the fair value of the common shares at the grant date. The options vest in accordance with terms as determined by our board of directors, typically over three to four years for options issued to employees and consultants, and over one tothree years for members of our board of directors. The expiry date for each option is set by our board of directors with a maximum expiry date of ten years from the date of grant. In addition, the 2010 Plan allows for accelerated vesting of outstanding equity awards in the event of a change in control. The terms for accelerated vesting, in the event of a change in control, is determined at our discretion and defined under the employment agreements for our officers and certain of our employees.

ASC 718 Compensation – Stock Compensation

We recognize expense related to the fair value of our stock-based compensation awards using the provisions of ASC 718. We use the Black-Scholes option pricing model as the most appropriate fair value method for our stock options and recognize compensation expense for stock options on a straight-line basis over the requisite service period. In valuing our stock options using the Black-Scholes option pricing model, we make assumptions about risk-free interest rates, dividend yields, volatility and weighted average expected lives, including estimated forfeiture rates of the options.

The expected life was calculated based on the simplified method as permitted by the SEC's Staff Accounting Bulletin 110, Share-Based Payment. We consider the use of the simplified method appropriate because of the lack of sufficient historical exercise data. The computation of expected volatility was based on the historical volatility of comparable companies from a representative peer group selected based on industry and market capitalization. The risk-free interest rate is based on a U.S. Treasury instrument whose term is consistent with the expected life of the stock options. In addition to the assumptions above, as required under ASC 718, management made an estimate of expected forfeitures and is recognizing compensation costs only for those equity awards expected to vest. Forfeiture rates are estimated using historical actual forfeiture rates. These rates are adjusted on a quarterly basis and any change in compensation expense is recognized in the period of the change. We have never paid or declared cash dividends on our common stock and do not expect to pay cash dividends in the foreseeable future.

The estimated fair value of stock options granted in the respective periods was determined using the Black-Scholes option pricing model using the following weighted average assumptions:

	2021	2020
Risk-free interest rates	0.66%	0.94%
Expected dividend yield	0%	0%
Expected life	6.00 years	6.00 years
Expected volatility	110.10%	108.78%
Forfeiture rate	0%	0%

The weighted average fair value of stock options granted during the year ended December 31, 2021 was $9.96.

The results for the periods set forth below included stock-based compensation expense in the following expense categories of the consolidated statements of loss (in thousands):

	Year ended December 31,	
	2021	2020
Research and development	$ 685	$ 403
General and administrative	1,502	883
Total stock-based compensation	$ 2,187	$ 1,286

Stock option transactions and the number of stock options outstanding are summarized below:

	Number of Optioned Common Shares	Weighted Average Exercise Price
Balance, January 1, 2021	**227,442**	$ 44.64
Granted	294,650	12.07
Expired	(2)	39,204.00
Balance, December 31, 2021	**522,090**	**$ 26.11**

The following table summarizes information about stock options outstanding at December 31, 2021 regarding the number of ordinary shares issuable upon: (1) outstanding options and (2) vested options.

(1) Number of common shares issuable upon exercise of outstanding options:

Exercise Prices	Number of Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Life (in years)
$7.20 - $9.25	50,500	$ 7.48	9.49
$9.26 - $10.13	11,250	9.90	9.36
$10.14 - $10.78	98,000	10.36	8.88
$10.79 - $11.65	74,880	11.20	8.08
$11.66 - $12.60	5,650	12.10	9.20
$12.61 - $20.74	232,750	13.09	9.07
$20.75 - $39.80	14,766	28.40	7.08
$39.81 - $59.30	18,747	51.20	6.72
$59.31 - $67.50	8,087	67.40	6.57
$67.51 - $28,952.00	7,460	837.69	6.00
	522,090	**$ 26.11**	**8.72**

(2) Number common shares issuable upon exercise of vested options:

Exercise Prices	Number of Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Life (in years)
$7.20 - $9.25	5,500	$ 8.60	8.36
$9.26 - $10.13	—	—	—
$10.14 - $10.78	—	—	—
$10.79 - $11.65	35,937	11.20	8.08
$11.66 - $12.60	1,413	12.10	9.20
$12.61 - $20.74	—	—	—
$20.75 - $39.80	11,862	28.40	7.08
$39.81 - $59.30	15,839	51.20	6.72
$59.31 - $67.50	6,939	67.40	6.57
$67.51 - $28,952.00	7,332	851.13	5.98
	84,822	**$ 98.12**	**7.42**

As at December 31, 2021, and December 31, 2020, the total unrecognized compensation expense related to stock options granted was $.4 million and $2.2 million, respectively, each of which is expected to be recognized into expense over a period of approximately 2.56 years.

The aggregate intrinsic value of options exercised was calculated as the difference between the exercise price of the stock options and the fair value of the underlying common stock as of the date of exercise. The aggregate intrinsic value of options exercised for the years ended December 31, 2021, 2020 and 2019 was zero, zero and zero, respectively. At December 31, 2021, the aggregate intrinsic value of the outstanding options was $19,500 and the aggregate intrinsic value of the exercisable options was zero.

[d] Restricted Stock Unit Awards

We grant restricted stock unit awards that generally vest and are expensed over a four-year period. We also grant restricted stock unit awards that vest in conjunction with certain performance conditions to certain executive officers and key employees. At each reporting date, we are required to evaluate whether achievement of the performance conditions is probable. Compensation expense is recorded over the appropriate service period based upon our assessment of accomplishing each performance provision. For the years ended December 31, 2021, 2020 and 2019, $0.4 million, $0.1 million and $0.4 million, respectively, of stock based compensation expense was recognized related to these awards.

The following table summarizes our restricted stock unit award activity during the year ended December 31, 2021:

	Number of Shares	Weighted Average Grant Date Fair Value
Balance, January 1, 2021	**231**	**$ 580.00**
Granted	53,250	13.09
Released	(231)	580.00
Balance, December 31, 2021	**53,250**	**$ 13.09**

As of December 31, 2021, we had approximately $0.4 million in total unrecognized compensation expense related to our restricted stock unit awards which is to be recognized over a weighted-average period of approximately 1.49 years.

[e] Stock Warrants

On May 30, 2019, we entered into a Warrant Exercise Agreement, or the Exercise Agreement, with an institutional investor. Pursuant to the Exercise Agreement, the investor exercised (i) outstanding warrants to purchase 13,515 shares of our common stock with an exercise price of $62.89 per share issued as part of the October 2018 financing and (ii) outstanding warrants to purchase 41,875 shares of our common stock with an exercise price of $80.00 per share issued as part of the June 2018 financing, for aggregate exercise proceeds to us of approximately $4.2 million, or, collectively, the Warrant Exercise.

As an inducement for the Warrant Exercise, we agreed to issue to the investor a new warrant, exercisable for six years, to purchase up to 60,000 shares of our common stock at an exercise price of $90 per share, or the New Warrant. We also agreed to file a registration statement covering the resale of the shares underlying the New Warrant Shares. The New Warrant and the shares underlying the New Warrant were offered to the investor in reliance upon the exemption provided by Rule 506 of Regulation D and Section 4(a)(2) of the Securities Act of 1933.

Under ASC 260, the fair value of the New Warrant of $3.9 million was recognized into accumulated deficit on our consolidated balance sheet as at June 30, 2019. We determined the fair value of the New Warrant using the Black-Scholes pricing model with the following assumptions: stock price of $84.6, volatility of 97.16%, risk-free interest rate of 2.06% and expected term of six years.

The following is a summary of outstanding warrants to purchase common stock at December 31, 2021:

	Total Outstanding and Exercisable		Exercise price per Share	Expiration Date
(1) Warrants issued in September 2017 financing	411	$	699.2000	March 2023
(2) Warrants issued in June 2018 financing	114,100	$	80.0000	June 2023
(3) Warrants issued in October 2018 financing	31,215	$	62.8900	October 2023
(4) Warrants issued in May 2019 financing	60,000	$	90.0000	May 2025
(5) Warrants issued in December 2019 financing	612,967	$	6.6000	December 2024
(6) Warrants issued in April 2020 financing	182,461	$	7.2400	April 2025
(7) Warrants issued in April 2020 financing	24,375	$	7.3200	April 2025
(8) Warrants issued in April 2020 financing	25,270	$	7.5900	April 2025
(9) Pre-Funded Warrants issued in August 2020 financing	142,857	$	0.0010	*
(10) Warrants issued in December 2020 financing	50,000	$	8.7500	December 2025

*The pre-funded warrants do not have an expiration date.

For the year ended December 31, 2021, warrants to purchase 47,084 shares, issued in the December 2019 financing, were exercised at a per unit price of $6.60, for proceeds of $0.3 million, and warrants to purchase 3,750 shares issued in the April 2020 financing were exercised for a per unit price of $7.32, for proceeds of $27,450. For the year ended December 31, 2020, 489,952 of the warrants issued in the December 2019 financing were exercised at a per unit price of $6.60, for proceeds of $3.2 million. As at December 31, 2021, all of our outstanding warrants are classified as equity.

[f] 401(k) Plan

We maintain a 401(k) plan. Our securities are not offered as an investment option. Our shares are prohibited for inclusion in our 401(k) plan, as well as any match of our shares to employee contributions.

[g] Loss per common share

The following table presents the computation of basic and diluted net loss attributable to common stockholders per share (in thousands, except per share and share amounts):

	Years ended December 31,		
	2021	2020	2019
Numerator			
Net loss	$ (33,152)	$ (14,730)	$ (16,395)
Denominator			
Weighted average number of common shares outstanding	8,119,836	2,718,909	412,320
Basic and diluted net loss per common share	$ (4.08)	$ (5.42)	$ (39.76)

As of December 31, 2021, a total of 1.8 million options, restricted stock units and warrants, respectively, have not been included in the calculation of potential common shares as their effect on diluted per share amounts would have been anti-dilutive. Additionally, the outstanding Convertible Debt due December 2023 is included in the calculation of diluted per share amounts only if its inclusion is dilutive for periods during which the notes were outstanding. As of December 31, 2021, the outstanding Convertible Debt was not included in the calculation of diluted per share amounts as its effect would have been anti-dilutive.

13. COMMITMENTS AND CONTINGENCIES

The following table summarizes our contractual obligations as of December 31, 2021 (in thousands):

	Total	Less than 1 year	1-3 years	3-5 years	More than 5 years
Vancouver office operating lease	$ 74	$ 51	$ 23	$ —	$ —
Total	$ 74	$ 51	$ 23	$ —	$ —

Leases

We have an operating lease for our corporate office.

Operating leases with a term of 12 months or longer are included in ROU assets, other current liabilities, and operating lease liabilities on our consolidated balance sheets. Finance leases are included in property and equipment, other current liabilities, and other long-term liabilities on our consolidated balance sheets.

Operating lease ROU assets and operating lease liabilities are recognized based on the present value of the future minimum lease payments over the lease term at commencement date. As most of our leases do not provide an implicit rate, we use the incremental borrowing rate of comparable companies from a representative peer group selected based on industry and market capitalization. The operating lease ROU asset also includes any lease payments made and excludes lease incentives and initial direct costs incurred. Our lease terms may include options to extend or terminate the lease when it is reasonably certain that we will exercise that option. Lease expense for minimum lease payments is recognized on a straight-line basis over the lease term.

Vancouver Lease Arrangements

We had an operating lease agreement for office space in Vancouver, Canada, which expired in January 2019. Pursuant to the operating lease agreement, we had the option to terminate the lease early without penalty at any time after January 1, 2017 so long as we provided three months prior written notice to the landlord. This lease was not renewed.

On November 19, 2018, we entered into a lease agreement for new office space in Vancouver, British Columbia, which commenced on February 1, 2019, and has a four-year term. Pursuant to this lease, we rent approximately 2,367 square feet of office space. The annual rent is approximately $0.1 million.

The future minimum annual lease payments under the Vancouver lease are as follows (in thousands):

2022	68
2023	6
Total	**$ 74**

Seattle Lease Arrangement

On December 11, 2017, we entered into a lease, or the Seattle Lease, with 520 Pike Street, Inc., or Pike, pursuant to which we leased approximately 3,187 square feet located at Suite 2250 at 520 Pike Tower, Seattle, Washington, 98101, which commenced on March 1, 2018. The Seattle Lease expired on March 1, 2021 and was not renewed.

Our monthly base rent for the premises started at approximately $11,685 which commenced on March 1, 2018 and increased on an annual basis up to approximately $12,397. In addition, we paid a security deposit to Pike in the amount of $37,192, which was subject to periodic reductions on the anniversary of the Seattle Lease. After the first anniversary of the Seattle Lease, we received a payment of $12,397 after the second anniversary, $12,397 from the security deposit was applied against one month of rent and on termination of the Seattle Lease, we received a payment of the $12,397 for the remaining amount of the security deposit. The Seattle Lease was classified as an operating lease.

Consolidated rent and operating expense relating to both the Vancouver, Canada and Seattle, Washington offices for years ended December 31, 2021, 2020 and 2019 was $0.1 million, $0.2 million and $0.2 million, respectively.

Other information related to leases was as follows:

	Year Ended December 31,	
	2021	2020
Supplemental Cash Flows Information		
Cash paid for amounts included in the measurement of lease liabilities:		
Operating cash flows from operating leases	$ 83	$ 186
Right-of-use assets obtained in exchange for lease obligations:		
Operating leases	—	—
Weighted Average Remaining Lease Term		
Operating leases	1.08 years	1.77 years
Weighted Average Discount Rate		
Operating leases	9.97 %	9.97 %

Guarantees and Indemnifications

We indemnify our officers, directors and certain consultants for certain events or occurrences, subject to certain limits, while the officer or director is or was serving at its request in such capacity. The term of the indemnification period is equal to the officer's or director's lifetime.

The maximum amount of potential future indemnification is unlimited; however, we have obtained director and officer insurance that limits our exposure and may enable us to recover a portion of any future amounts paid. We believe that the fair value of these indemnification obligations is minimal. Accordingly, we have not recognized any liabilities relating to these obligations as of December 31, 2021.

We have certain agreements with certain organizations with which it does business that contain indemnification provisions pursuant to which it typically agrees to indemnify the party against certain types of third-party claims. We accrue for known indemnification issues when a loss is probable and can be reasonably estimated. There were no accruals for or expenses related to indemnification issues for any period presented.

14. QUARTERLY FINANCIAL INFORMATION (UNAUDITED)

The following table summarizes the unaudited statements of operations for each quarter of 2021 and 2020 (in thousands, except per share amounts):

	March 31	June 30	September 30	December 31
2021				
Research and development	5,642	9,227	4,591	4,506
General and administrative	2,342	2,075	2,102	2,609
Total operating expenses	7,984	11,302	6,693	7,115
Other income (expense)	(15)	(9)	2	(36)
Net loss	(7,999)	(11,311)	(6,691)	(7,151)
Basic and diluted net loss per share	$ (1.30)	$ (1.53)	$ (0.71)	$ (0.76)
2020				
Research and development	1,541	1,103	1,891	2,347
General and administrative	1,816	1,815	1,863	2,374
Total operating expenses	3,357	2,918	3,754	4,721
Other income	37	(4)	(10)	(3)
Net loss	(3,320)	(2,922)	(3,764)	(4,724)
Basic and diluted net loss per share	$ (2.15)	$ (1.68)	$ (1.14)	$ (1.11)

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A. CONTROLS AND PROCEDURES

Evaluation of Disclosure Controls and Procedures

We maintain disclosure controls and procedures that are designed to ensure that material information required to be disclosed in our periodic reports filed or submitted under the Exchange Act, is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms. Our disclosure controls and procedures are also designed to ensure 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 principal executive officer and principal financial officer, as appropriate, to allow timely decisions regarding required disclosure.

We carried out an evaluation, under the supervision and with the participation of our management, including the principal executive officer and the principal financial officer, of the effectiveness of the design and operation of the disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act. Based on that evaluation, our principal executive officer and principal financial officer concluded that our disclosure controls and procedures were effective as of December 31, 2020.

Changes in Internal Control Over Financial Reporting

We have not made any changes to our internal control over financial reporting (as defined in Rule 13a-15(f) and 15d-15(f) under the Exchange Act) during the quarter ended December 31, 2021 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Management's Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over our financial reporting, as defined in Rule 13a-15(f) under the Exchange Act. Our internal control over financial reporting is a process designed under the supervision of our principal executive and principal financial officers to provide reasonable assurance regarding the reliability of financial reporting and the preparation of our financial statements for external reporting purposes in accordance with U.S. generally accepted accounting principles.

As of December 31, 2021, management assessed the effectiveness of our internal control over financial reporting based on the framework established in "Internal Control—Integrated Framework" issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) (2013 Framework). Based on this evaluation, management has determined that our internal control over financial reporting was effective as of December 31, 2021.

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.

ITEM 9B. OTHER INFORMATION

None.

ITEM 9C. DISCLOSURE REGARDING FOREIGN JURISDICTIONS THAT PREVENT INSPECTIONS

None.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by this Item is set forth in our 2021 Proxy Statement to be filed with the SEC within 120 days of December 31, 2021, and is incorporated by reference into this Annual Report on Form 10-K by reference.

ITEM 11. EXECUTIVE COMPENSATION

The information required by this Item is set forth in our 2021 Proxy Statement to be filed with the SEC within 120 days of December 31, 2021, and is incorporated by reference into this Annual Report on Form 10-K by reference**.**

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The following table sets forth certain information regarding our equity compensation plans as of December 31, 2021:

	(a)		(b)		(c)	
Plan category	Number of securities to be issued upon exercise of outstanding options, restricted stock units, 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))	
Equity compensation plans approved by security holders	575,340	(1)	$ 26.11	(1)	4,145	(1)
Equity compensation plans not approved by security holders(2)	45,000		7.35		—	
Total	620,340		$ 26.11		4,145	

(1) As of December 31, 2021, we maintained the following equity compensation plans, which were approved by security holders: (a) the 2010 Performance Incentive Plan, (b) the 2017 Equity Incentive Plan and (c) the 2018 Equity Incentive Plan.

(2) Stock options granted as an inducement to new employees for entering into employment agreements with us in accordance with Nasdaq Listing Rule 5635(c)(4).

The remaining information required by this Item is set forth in our 2021 Proxy Statement to be filed with the SEC within 120 days of December 31, 2021, and is incorporated by reference into this Annual Report on Form 10-K by reference.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

The information required by this Item is set forth in our 2021 Proxy Statement to be filed with the SEC within 120 days of December 31, 2021, and is incorporated by reference into this Annual Report on Form 10-K by reference.

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES

The information required by this Item is set forth in our 2021 Proxy Statement to be filed with the SEC within 120 days of December 31, 2021, and is incorporated by reference into this Annual Report on Form 10-K by reference.

PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

(1) Financial Statements

(2) All schedules are omitted because they are not required or the required information is included in the consolidated financial statements or notes thereto.

(3) Exhibits

Exhibit Number	Description	Incorporated by Reference				Filed/ Furnished Herewith
		Form	File No.	Exhibit	Filing Date	
3.1	Second Amended and Restated Certificate of Incorporation filed on May 24, 2013	8-K	033-80623	3.1	May 29, 2013	
3.2	Certificate of Amendment to Amended and Restated Certificate of Incorporation filed on May 21, 2015	8-K	033-80623	3.1	May 22, 2015	
3.3	Certificate of Amendment (Reverse Stock Split) to Second Amended and Restated Certificate of Incorporation filed on August 1, 2017	8-K	033-80623	3.1	August 2, 2017	
3.4	Certificate of Amendment (Name Change) to Second Amended and Restated Certificate of Incorporation filed on August 1, 2017	8-K	033-80623	3.2	August 2, 2017	
3.5	Certificate of Amendment (Elimination of Cumulative Voting) to Second Amended and Restated Certificate of Incorporation filed on October 31, 2017	8-K	033-80623	3.1	November 1, 2017	
3.6	Certificate of Amendment (Reverse Stock Split) to the Second Amended and Restated Certificate of Incorporation filed on May 22, 2018	8-K	033-80623	3.1	May 23, 2018	
3.7	Certificate of Amendment (Increase in Authorized Shares) to the Second Amended and Restated Certificate of Incorporation filed on May 22, 2018	8-K	033-80623	3.2	May 23, 2018	
3.8	Certificate of Designation of Preferences, Rights and Limitations, with respect to the Series B Convertible Preferred Stock, filed	8-K	033-80623	3.1	December 20, 2019	
3.9	Sixth Amended and Restated Bylaws	8-K	033-80623	3.1	January 5, 2017	
3.10	Amendment to Sixth Amended and Restated Bylaws	10-Q	033-80623	3.1	November 7, 2018	

Exhibit Number	Description	Incorporated by Reference				Filed/ Furnished Herewith
		Form	File No.	Exhibit	Filing Date	
4.1	Specimen Certificate of Common Stock	10-Q	000-21243	4.1	November 10, 2008	
4.2	Form of Warrant (LPC)	8-K	033-80623	4.1	September 14, 2017	
4.3	Form of Common Stock Purchase Warrant (June 2018 Offering)	8-K	033-80623	4.1	June 20, 2018	
4.4	Form of Preferred Stock Certificate	8-K	033-80623	4.2	June 20, 2018	
4.5	Form of Common Stock Purchase Warrant (October 2018 Private Placement)	8-K	033-80623	4.1	October 1, 2018	
4.6	Form of Warrant (May 2019)	8-K	033-80623	4.1	June 3, 2019	
4.7	Form of Common Stock Purchase Warrant (December 2019 Offering)	8-K	033-80623	4.1	December 20, 2019	
4.8	Form of Common Stock Purchase Warrant (April 2020)	8-K	033-80623	4.1	April 30, 2020	
4.9	Form of Pre-Funded Warrant (August 2020)	8-K	033-80623	4.1	August 4, 2020	
4.10	Form of Underwriter's Warrant	S-1	333-250074	4.11	November 30, 2020	
4.11	Description of Securities Registered Under Section 12 of the Securities Exchange Act of 1934	10-K	033-80623	4.12	March 13, 2020	
4.12	Form of Debt Security (December 2021)	S-3	333-261811	4.12	December 21, 2021	
4.13	Form of Indenture (December 2021)	S-3	333-261811	4.13	December 21, 2021	
4.14	Registration Rights Agreement, dated December 22, 2021, among Achieve Life Sciences, Inc., Silicon Valley Bank and SVB Innovation Credit Fund VIII, L.P.	8-K	033-80623	10.1	December 22, 2021	
10.3	OncoGenex Technologies Inc. Amended and Restated Stock Option Plan††	F-1	333-139293	10.1	December 13, 2006	
10.4	Form of OncoGenex Pharmaceuticals, Inc. 2010 Stock Option Agreement††	8-K	033-80623	10.1	June 14, 2010	
10.5	Form of OncoGenex Pharmaceuticals, Inc. 2010 Restricted Stock Unit Agreement††	10-Q	033-80623	10.2	November 3, 2011	
10.6	OncoGenex Pharmaceuticals, Inc. 2010 Performance Incentive Plan, as amended and restated††	DEF 14A	033-80623	Appendix A	April 16, 2015	
10.7a	Achieve Life Sciences 2017 Equity Incentive Plan††	DEF 14A	033-80623	Appendix A	September 21, 2017	
10.7b	Form of Achieve Life Sciences Stock Option Agreement††	10-Q	033-80623	10.7b	March 1, 2018	
10.7c	Form of Achieve Life Sciences Restricted Stock Unit Agreement††	10-Q	033-80623	10.7c	March 1, 2018	
10.8	Achieve Life Sciences 2017 Employee Stock Purchase Plan††	DEF 14A	033-80623	Appendix B	September 21, 2017	

Exhibit Number	Description	Incorporated by Reference				Filed/ Furnished Herewith
		Form	File No.	Exhibit	Filing Date	
10.9	Achieve Life Sciences 2018 Equity Incentive Plan, and forms of award agreements thereunder††	10-Q	033-80623	10.1	November 7, 2018	
10.10	Form of Indemnification Agreement for Officers and Directors of the Company†† (p)	S-1	33-96112	10.19	September 25, 1995	
10.11	Form of Indemnification Agreement between OncoGenex Technologies Inc. and Cindy Jacobs††	F-1	333-139293	10.7	December 13, 2006	
10.12	Employment Agreement between the Company and Cindy Jacobs dated as of November 3, 2009††	10-Q	033-80623	10.27	November 5, 2009	
10.13	Employment Agreement between OncoGenex Pharmaceuticals, Inc. and John Bencich††	10-Q	033-80623	10.1	November 10, 2016	
10.14	Employment Agreement between the Company and Richard Stewart, executed May 22, 2018 ††	8-K	033-80623	10.1	May 23, 2018	
10.15	Employment Agreement between the Company and Anthony Clarke, executed May 22, 2018 ††	8-K	033-80623	10.2	May 23, 2018	
10.16	Exclusive License Agreement, by and between Sopharma Joint Stock Company and Extab Corporation, dated May 26, 2009*	S-4/A	333-216961	10.21	May 3, 2017	
10.17	Variation of Contract, by and between Sopharma AD and Extab Corporation, dated May 14, 2015*	S-4/A	333-216961	10.22	May 3, 2017	
10.18	Commercial Agreement on Supply of Pharmaceutical Products, by and between Sopharma AD and Extab Corporation, dated February 1, 2010*	S-4/A	333-216961	10.23	May 3, 2017	
10.19	Variation of Contract, by and between Sopharma AD and Extab Corporation, dated May 14, 2015*	S-4/A	333-216961	10.24	May 3, 2017	
10.20	Technical and Quality Agreement, by and between Sopharma AD and Extab Corporation, dated May 14, 2015*	S-4/A	333-216961	10.25	May 3, 2017	

Exhibit Number	Description	Incorporated by Reference				Filed/ Furnished Herewith
		Form	File No.	Exhibit	Filing Date	
10.21	License of Technology, by and between University of Bristol and Achieve Life Science, Inc., dated July 13, 2016*	S-4/A	333-216961	10.27	May 3, 2017	
10.22	Amendment to University of Bristol License Agreement, dated January 22, 2018, by and between Achieve Life Science, Inc., and the University of Bristol*	10-Q/A	033-80623	10.1	May 23, 2018	
10.24	Office Lease by and between 0846869 B.C. Ltd. and Achieve Life Sciences Technologies Inc., commencing February 1, 2019.	10-K	033-80623	10.25	March, 14, 2019	
10.25	Purchase Agreement, by and between Achieve Life Sciences, Inc. and Lincoln Park Capital Fund, LLC. dated as of September 14, 2017	8-K	033-80623	10.1	September 14, 2017	
10.26	Amendment No. 1 to Purchase Agreement, by and between Achieve Life Sciences, Inc. and Lincoln Park Capital Fund, LLC. dated as of September 14, 2017	10-K	033-80623	10.27	March 13, 2020	
10.27	Amended and Restated Supply Agreement, dated July 28, 2017, by and between Achieve Life Science, Inc., and Sopharma AD*	10-Q	033-80623	10.1	November 9, 2017	
10.28	Letter of Variation, dated September 28, 2020, by and between Achieve Pharma UK Limited and Richard Stewart††	10-Q	033-80623	10.1	November 12, 2020	
10.29	Letter of Variation, dated September 28, 2020, by and between Achieve Pharma UK Limited and Anthony Clark††	10-Q	033-80623	10.2	November 12, 2020	
10.30	Amended and Restated Employment Agreement, dated September 28, 2020, by and between Achieve Life Sciences, Inc. and John Bencich ††	10-Q	033-80623	10.3	November 12, 2020	
10.31	Amended and Restated Employment Agreement, dated September 28, 2020, by and between Achieve Life Sciences, Inc. and Cindy Jacobs ††	10-Q	033-80623	10.4	November 12, 2020	
10.32	At the Market Sales Agreement, dated December 21, 2021, by and between Achieve Life Sciences, Inc. and Virtu Americas LLC	S-3	333-261811	1.2	December 21, 2021	
10.33	Contingent Convertible Debt Agreement, dated December 22, 2021, among Achieve Life Sciences, Inc., Silicon Valley Bank and SVB Innovation Credit Fund VIII, L.P.	8-K	033-80623	10.1	December 22, 2021	
21.1	Subsidiaries of the Registrant					X

Exhibit Number	Description	Incorporated by Reference				Filed/ Furnished Herewith
		Form	File No.	Exhibit	Filing Date	
23.1	Consent of PricewaterhouseCoopers LLP					X
24.1	Power of Attorney (included on the signature page hereto)					
31.1	Certification of Chief Executive pursuant to Rule 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002					X
32.1	Certification of Chief Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002**					X
101.INS	Inline XBRL Instance Document					X
101.SCH	Inline XBRL Taxonomy Extension Schema Document					X
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document					X
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document					X
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document					X
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document					X
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)					X

† Schedules and similar attachments to the Merger Agreement have been omitted pursuant to Item 601(b)(2) of Regulation S-K. The Company will furnish supplementally a copy of any omitted schedule or similar attachment to the SEC upon request.

†† Indicates management contract or compensatory plan or arrangement.

* The Company has omitted portions of the exhibit as permitted under Item 601(b)(10) of Regulation S-K.

** The certifications attached as Exhibits 32.1 and 32.2 accompany to this Annual Report on Form 10-K pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, and shall not be deemed filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended.

SIGNATURES

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

ACHIEVE LIFE SCIENCES, INC.
(Registrant)

Date: March 10, 2022

By: /s/ JOHN BENCICH
John Bencich
Chief Executive Officer

Power of Attorney

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints John Bencich and Richard Stewart, jointly and severally, as such person's attorneys-in-fact, each with the power of substitution, for such person in any and all capacities, to sign any amendments to this Annual Report on Form 10-K, and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each of said attorneys-in-fact, or his substitute or substitutes, may do or cause to be done by virtue hereof.

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

By: /s/ JOHN BENCICH John Bencich	Chief Executive Officer and Director (Principal Executive Officer and Financial Officer)	Date: March 10, 2022
By: /s/ JERRY WAN Jerry Wan	Senior Director of Accounting Operations (Principal Accounting Officer)	Date: March 10, 2022
By: /s/ RICHARD STEWART Richard Stewart	Executive Chairman and Director	Date: March 10, 2022
By: /s/ CINDY JACOBS Cindy Jacobs	Chief Medical Officer	Date: March 10, 2022
By: /s/ DONALD JOSEPH Donald Joseph	Director	Date: March 10, 2022
By: /s/ MARTIN MATTINGLY Martin Mattingly	Director	Date: March 10, 2022
By: /s/ BRIDGET MARTELL Bridget Martell	Director	Date: March 10, 2022
By: /s/ JAY MOYES Jay Moyes	Director	Date: March 10, 2022
By: /s/ JAY MOYES Jay Moyes	Director	Date: March 10, 2022

Exhibit 21.1

SUBSIDIARIES OF THE REGISTRANT

Achieve Life Sciences Technologies Inc., incorporated under the federal laws of Canada

Achieve Life Science Inc., a Delaware Corporation

Extab Corporation, a Delaware Corporation

Achieve Pharma UK Limited, a Limited Company in the United Kingdom

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-8 (File Nos. 333-153206, 333-168820, 333-190480, 333-197937, 333-206569, 333-221473, 333-228253, 333-231520, 333-236059, 333-238505, and 333-254156), Form S-1 (File Nos. 333-232817, 333-228596, 333-234530, 333-238970 and 333-250074) and Form S-3 (File Nos. 333-207670, 333-229019, and 333-261811) of Achieve Life Sciences, Inc. of our report dated March 10, 2022 relating to the consolidated financial statements, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP

Chartered Professional Accountants
Vancouver, Canada
March 10, 2022

Exhibit 31.1

Certification Pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934

I, John Bencich, certify that:

1. I have reviewed this annual report on Form 10-K of Achieve Life Sciences, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officers and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

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

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

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

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

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

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

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

Date: March 10, 2022

/s/ JOHN BENCICH
John Bencich
Chief Executive Officer (Principal Executive and Financial Officer)

Exhibit 32.1

Certification pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002

I, John Bencich, Chief Executive Officer and Principal Executive and Financial Officer of Achieve Life Sciences, Inc. (the "Company"), certify, pursuant to Rule 13a-14(b) or Rule 15d-14(b) of the Securities Exchange Act of 1934 and 18 U.S.C. Section 1350, that:

(1) the Annual Report on Form 10-K of the Company for the year ended December 31, 2021 (the "Report") fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934 (15 U.S.C. 78m or 780(d)); and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 10, 2022

/s/ JOHN BENCICH
John Bencich
Chief Executive Officer (Principal Executive and Financial Officer)